



CENTER FOR CONTINUING PROFESSIONAL DEVELOPMENT

مركز التطوير المهني المستمر





Media Fill

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1. Introduction
2. Definition
3. Media fill simulation
4. Study design
5. conclusion

Introduction - Purpose of GMP



- Generally, good GMP-compliance is based on good understanding

- When you understand the reasons for a particular GMP requirement, the chances are high that you will be able to comply with it – in procedures , records and actions

- In this session we will understand what GMP intends to gain from media fills



What & Why Media Fill ?



• The basic idea is that we run an aseptic process, substituting a microbiologically inert placebo for product

– And then test every unit for microbiological contamination

• It has been convenient that liquid microbiological media serve as placebo

– This is because we can inspect each filled unit by eye for visible growth



Media Fill Definition …… FDA



- This process simulation, also known as a media fill, normally includes exposing the microbiological growth medium to product contact surfaces of equipment, container closure systems, critical environments, and process manipulations to closely simulate the same exposure that the product itself will undergo.

- The sealed containers filled with the medium are then incubated to detect microbial contamination

Media Fill Purpose ……… PIC/s



- Process simulation studies (media fills) are simulating the whole process in order to evaluate the sterility confidence of the process.

- Process simulation studies include formulation (compounding), filtration and filling with suitable media.

- Simulations are made to ensure that the regular process for commercial batches repeatedly and reliably produces the finished product of the required quality.



Activity
Before starting media fill ……….



- An aseptic process incorporates many systems to assure and control sterility of the materials produced;
  What are these systems?



Before starting media fill ……….



- An aseptic process incorporates many systems to assure and control sterility of the materials produced;

These systems include:

- Product, equipment and component sterilization
- Personnel training and certification of aseptic gowning and aseptic techniques
- Equipment and facility sanitization programs
- Environmental system: microbial levels, differential pressure, air pattern, velocity, temperature and humidity, air supply
- Personnel, material and equipment flows
- Standard operating procedures/work instructions or their equivalent.
- A underlying quality system approach to process control
- Primary packaging components should be prepared the same as for normal production runs (washing and sterilization)

Media Fill Simulation



1. Study Design
2. Operator training /qualification
3. Frequency and Number of Runs
4. Duration of Runs
5. Size of Runs
6. Filling equipment





Media Fill Simulation



7-Filling volume

8-Line Speed

9-Environmental Conditions

10-Media

11-Media

12-Incubation and Examination of Media-Filled Units

13-Interpretation of Test Results

14- general Nots

15- Media fill-typical inspection



1. Study Design



- A media fill program should incorporate the contamination risk factors that occur on a production line, and accurately assesses the state of process control.
- Should not reflect a better condition than that present during the manufacturing process.
- Should closely simulate aseptic manufacturing operations incorporating, as appropriate, worst-case activities and conditions that provide a challenge to aseptic operations.
- Bracketing principles can be applied to reduce number of fills.
- Lyophilization , when applicable.
- Number of personnel and their activities



Activity
1. Study Design interventions



- ***What are the type of Interventions during media fill ?***



Activity
1. Study Design interventions



<u>Interventions – both routine and non-routine</u>

- The interventions should simulate what occurs in a production run; media fill records should document all interventions performed and the number of units removed.

❑ **Routine interventions:**

- aseptic line set-up in which sterilised parts are removed from protective materials and installed is a potential danger; it is common to identify the first containers filled as they may be more indicative of potential problem with aseptic assembly.

- Other routine interventions:
  - stoppers bowl feeding,
  - remove jam stoppers,
  - gloves change,
  - Max. holding time of sterilized items (gown- tools)
  - remove fallen vials,
  - operators breaks,
  - environmental monitoring.

1. Study Design



<u>Interventions – both routine and non-routine</u>

- The inclusion and frequency of interventions in the APS should be based on assessed risks posed to product sterility

1. Study Design



<u>Interventions – both routine and non-routine</u>

- In no case should more units be removed during a media fill intervention than would be cleared during a production run , For example, if a production procedure requires removal of 10 units after an intervention at the stoppering station infeed, batch records (i.e., for production and media fills) should clearly document conformance with this procedure.

- ❑ **Non routine interventions (occur randomly):** glass breakage, change / reset of filling needles, interventions on weight adjustments, sensor failure, rail adjustments.
- ❑ The APS should take into account various aseptic manipulations and interventions known to occur during normal production, as well as worstcase situations, and should take into account the following: i. Inherent and corrective interventions representative of the routine process should be performed in a manner and frequency similar to that during the routine aseptic process. ii. The inclusion and frequency of interventions in the APS should be based on assessed risks posed to product sterility

1. Study Design activity



<u>Interventions – both routine and non-routine</u>

What is the items taken in to consideration during recording interventions in media fill batch record?



1. Study Design



Interventions – both routine and non-routine

What is the items taken in to consideration during recording interventions in media fill batch record?

- Aseptic process step:time (start– end)
- Intervention type
- Name of intervention
- intervention time: start –end
- Position of filled units during intervention in racks (coding and numbering of rack carrying filled units)

2-Operators Training / Qualification - General Principles





- Training Plan must be available (authorized by QA),
- Beside on-the-job training: surveillance how persons are behavior in Class A/B conditions,
- Operator, Supervisor should have been adequately trained as well as the manager in Aseptic Considerations – Interventions (allowable and non-allowable) – SOP: removal of product during interventions – GMP – Guidelines – Hygiene – Cleanroom behavior
- Manager and Supervisor should have oversight over training plan and performance,
- QC and Maintenance persons: almost same requirements.



2-Operators Training / Qualification - General Principles



- Each operator performing aseptic processes are requested to participate in media fill.
- Set-up and line operators should be part of not less than one process simulation per year.
- Operators such as line mechanics and environmental samplers should be managed in a similar manner.
- A maximum number of personnel present in the aseptic processing room should be established.



3.Number of runs & Frequency







- ❖ Start-up simulation is applicable to :
  - new processes,
  - new equipment
  - after critical changes to environment , equipment, process
  - significant personnel changes.
- At least three consecutive separate successful runs should be performed during initial line qualification.

- ❖ Routine semi-annual qualification conducted for each processing line will evaluate the state of control of the aseptic process.

3.Number of runs & Frequency



❖ Revalidation

- Each change to a product or line change should be evaluated using a written change control system.

- Any changes or events that have the potential to affect the ability of the aseptic process to exclude contamination from the sterilized product should be assessed through additional media fills.

- For example,

- facility and equipment modifications,
- line configuration changes,
- significant changes in personnel,
- container closure system changes
- extended shutdowns
- anomalies in environmental testing results
- end product sterility testing showing contaminated products may be cause for revalidation of the system.

4.Duration of Run



- The duration of the media fill run should be determined by:

- The time it takes to incorporate manipulations and interventions, as well as appropriate consideration of the duration of the actual aseptic processing operation.
- the longest permitted run on the processing line can pose contamination risk (e.g., operator fatigue).
- Interventions that commonly occur should be routinely simulated, while those occurring rarely can be simulated periodically.
- For very large batches or long campaigns, some blank units (either empty or water filled) are used to maintain operating conditions during the simulation.
- When a firm operates on multiple shifts, the second and third shift should be included in the media fill programme.

5.Size of Run



- The number of containers used for media fills should be sufficient to enable a valid evaluation.
- For small batches less than 5,000 unit ----- the number of containers for media fills should at least equal the size of the product batch.
- Normal batch size from 5,000 to 10,000 unit ------the number of contains of media fill should be 5,000 - 10,000 unit.
- Normal batch size is more than 10,000 unit -------the number of contains of media fill should be larger than 10,000 unit.
- In contrast, a process conducted in an isolator can have a low risk of contamination because of the lack of direct human intervention and can be simulated with a lower number of units as a proportion of the overall operation.

5.Size of Run



Production batch description	Production batch size (# filled containers)	Minimum APS batch size (# of filled containers of media)	Recommendations
Small scale	≤ 5,000 units	≤ 5,000 units	APS batch size should be at least equal to production batch size.
Mid-scale	5,000 to 10,000 units	5,000 to 10,000 units	APS batch size should be of comparable size to the production batch size. For high speed filling or with maximum size production batches, it may be appropriate to fill additional units in order to accommodate normal aseptic manipulations, interventions, and realistic simulation of the process.
Large scale	> 10,000 units	> 10,000 units A variety of approaches can be employed to evaluate the process. See guidance below.	See guidance below
Manual Fill	Any amount	Same as production batch size	APS batch size should be at least equal to production batch size. Entire manual filling operation represents an intervention which should be captured.

5.Size of Run



- ***<u>For large production batches the following approaches may be considered for the APS batch size and approach.</u>***

- Alternate between Media Filled and Empty Units

- Operate the line without filling media into all of the containers.

- Media should be filled periodically throughout the process including at the beginning, and end of the routine process duration, as well as during and immediately after any planned intervention.

5.Size of Run



For large production batches the following approaches may be considered for the APS batch size and approach.

- Alternate between WFI Filled and Media Filled units

– Follow the approach described above, except fill units with WFI when not filling with media.

– The impact of media dilution with WFI which could alter the growth promoting characteristics must be considered.

6-Filling Equipment



- The same equipment that is used for product fills should be used for media fills.

- If inert gases are normally used in the process, filtered air should be applied during media fills not to prohibit growth of microorganisms. (If anaerobic microorganisms are found during routine E.M., the use of inert gases should also be considered.)

- All aseptic holding vessels should be part of a regular process simulation test, unless a validated pressure hold or vacuum hold test is routinely performed.



7-lyophilization simulation



The process simulation procedure for lyophilized products should represent the entire aseptic processing chain, including filling, transport, loading, a representative duration of the chamber dwell, unloading and sealing under specified, documented and justified conditions representing worst-case operating parameters



7-lyophilization simulation



- For lyopholization operations, FDA recommends that;

- unsealed containers be exposed to partial evacuation of the chamber in a manner that simulates the process.

- Vials should not be frozen, and precautions should be taken that ensure that the medium remains in an aerobic state to avoid potentially inhibiting the growth of microorganisms.

7-lyophilization simulation



The lyophilization process simulation should mimic all aspects of the process, except those that may affect the viability or recovery of contaminants.

For instance, boiling over or actual freezing of the solution should be avoided.

Factors to consider in determining APS design include, where applicable:

– the use of air to break vacuum instead of nitrogen or other process gases;

– replicating the maximum interval between sterilization of the lyophilizer and its use;

– replicating the maximum period of time between filtration and lyophilization;

– quantitative aspects of worst-case situations, for example, loading the largest number of trays, replicating the longest duration of loading where the chamber is open to the environment.

8-Fill volume



- The volume of media filled into the containers need not the routine fill volume.
- It should be sufficient to contact the container-closure seal surfaces (when the unit is inverted and swirled) and sufficient to allow visual detection of microbial growth post incubation.
- Smaller containers should not be over-filled as sufficient air must be available in the container headspace to support the growth of aerobic organisms (generally 25% of volume is not filled).
- Clear containers should be used as a substitute for amber containers to allow visual detection of microbial growth

9.Line speed



- The media fill program should adequately address the range of line speeds employed during production.

- Each media fill run should evaluate a single line speed, and the speed chosen should be justified.

- For example, use of high line speed is often most appropriate in the evaluation of manufacturing processes characterized by frequent interventions or a significant degree of manual manipulation.

- The largest container (often filled at the lowest speed because of its large fill volume) often has the large opening , so the potential for microbial entry from the environment should be the greatest for that size.

- The smallest container (often filled at the highest speed for its lower fill volume) represents the greatest handling difficulty; the smaller container are more fragile and less stable and be more subjected to breakage and jamming in the equipment.

10.Environmental Conditions



- Permit stressful conditions (e.g., maximum number of personnel present and elevated activity level)
- Stressful conditions do not include artificially created environmental extremes, such as reconfiguration of HVAC systems to operate at worst-case limits.
- Air sampling using either active and passive sampling methods should be performed during the execution of the process.
- Surface sampling is best performed at the end of aseptic process. Also personnel should be monitored
- Microbiological monitoring (air, surfaces, personnel) and particle monitoring should be performed during media fill employing the same procedure in force
- Sometimes the number of sampling locations might be increased respect the routine procedure

11.Media



- The selected nutrient medium should be capable of growing a designated group of reference microorganisms, as described by the relevant pharmacopoeia, and suitably representative local isolates.

11.Media



- In general, Guidance notes the use of Soybean Casein Digest Medium (SCDM) also known as tryptone soya broth (TSB)., should be used.

- Use of anaerobic growth media (e.g., fluid thioglycollate medium) should be considered in special circumstances.



- The media selected should be able to support the growth of a wide range of microorganisms.

  demonstrated to promote growth of gram positive and gram-negative bacteria, and yeast and mold .

- It is important that medium supplier can provide the certification for confirming materials are sourced from “BSE-free” countries.

11-Media



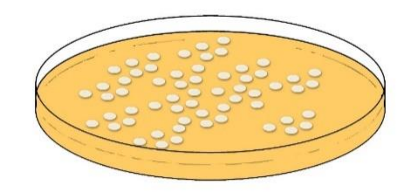
- The hold time between compounding of the media and filtration of media into a sterile vessel should be minimized.

- Media held in less than fully sterile conditions will immediately begin to support the growth of bioburden organisms that may be present.

- The medium should be suitable from a process perspective to perform as product (e.g. it should be filterable, if the product is normally also filtered).

- The medium should be clear in order to be able to observe any turbidity caused by growth.

- The medium should be prepared according to manufacturer’s instructions.



12.Incubation and Examination of Media-Filled Units



- Any filled units should be inspected prior to incubation; any defects that compromise the container closure or non-integral units are rejected and documented.

- All integral units from the APS should be incubated and evaluated, including units with cosmetic defects
- When a firm performs a final product inspection of units immediately following the media fill run, all integral units should proceed to incubation.

- Units found to have defects not related to integrity (e.g., cosmetic defect) should be incubated; units that lack integrity should be rejected, or those that have gone through non-destructive in-process control checks.

-

12.Incubation and Examination of Media-Filled Units



- Filled APS units should be agitated, swirled or inverted before incubation to ensure contact of the medium with all interior surfaces in the container.

- Filled APS units should be incubated without delay to achieve the best possible recovery of potential contamination. The selection of the incubation conditions and duration should be scientifically justified and validated to provide an appropriate level of sensitivity of detection of microbial contamination

12.Incubation and Examination of Media-Filled Units



- Units are incubated in an inverted position for the first half of the incubation period and then returned to an upright position for the remainder.
- Incubation temperature should be suitable for recovery of bioburden and environmental isolates and should at no time be outside the range of 20-35° C.
- Incubation temperature should be maintained within +2.5° C of the target temperature.
- Incubation time should not be less than 14 days

12.Incubation and Examination of Media-Filled Units



- Growth promotion testing of the media used in simulation studies should be carried out on completion of the incubation period to demonstrate the ability of the media to sustain growth if contamination is present.

- some vials (taken from the beginning, at half and at the end of the process) are inoculated with < 100 CFU and incubated for 3 days (bacteria) and 5 days (yeast and mould).

12.Incubation and Examination of Media-Filled Units



- Additional container shall be filled solely with sterile liquid medium for use as a negative control to confirm adverse conditions.

- Sample of empty containers is also to be closed and capped to be collected for sterility test to ensure proper sterilization of the empty vials before filling.

- Additional containers shall be filled solely with lactose monohydrate for use as a negative control to confirm adverse condition.

12.Incubation and Examination of Media-Filled Units



Filled APS units should be inspected by personnel who have been appropriately trained and qualified for the detection of microbiological contamination.

Inspection should be conducted under conditions that facilitate the identification of any microbial contamination..

Samples of the filled units should undergo positive control by inoculation with a suitable range of reference organisms and suitably representative local isolates.

13.Interpretation of Test Results



- When filling fewer than 5,000 units,

-- No contaminated units should be detected.

-- One (1) contaminated unit is considered cause for revalidation, following an investigation.

- When filling from 5,000 to 10,000 units:

-- One (1) contaminated unit should result in an investigation, including consideration of a repeat media fill.

-- Two (2) contaminated units are considered cause for revalidation, following investigation.

- When filling more than 10,000 units:

-- One (1) contaminated unit should result in an investigation.

-- Two (2) contaminated units are considered cause for revalidation, following investigation.

14-Media Fill Failures



• Separate SOP for Media Fill Failures Investigation

– Each contamination must be investigated. Microorganisms isolated from contaminated units should be identified to the species level when practical, to assist in the determination of the likely source of the contaminant.

– Repeat media fill or repeat validation, after investigation, depending on the level of contamination and the run size.

– General consensus: DO NOT perform repeat of Media Fill until (most probable) Root Cause is known/identified

•An aseptic process should be subject to a repeat of the initial validation when: i. the specific aseptic process has not been in operation for an extended period of time; ii. there is a change to the process, equipment, procedures or environment that has the potential to affect the aseptic process or an addition of new product containers or container-closure combinations

14-Media Fill Failures Investigation Steps



- A basic checklist for performing a media fill investigation can be derived from guidelines (e.g. PDA) and other publications/ presentations on this topic,

example:

- – Identification of the organism(s) in the contaminated units and in the environment (air, surfaces, personnel) and check for matching.
- – Check of media fill process documentation (batch records, deviations, filter integrity testing, cleaning, sanitization and sterilization records) for abnormalities.
- – Check of critical systems (HVAC and pressure cascade, HEPA filters, WFI/ PW, Compressed gasses, Clean Steam) and their maintenance/calibration records.
- – Verification of personnel training and aseptic qualification records.
- – Check of Validation and Change management records of the equipment and systems involved in the process, including holding times of sterilized materials.

15- Revalidation



- An aseptic process should be subject to a repeat of the initial validation when: i. the specific aseptic process has not been in operation for an extended period of time; ii. there is a change to the process, equipment, procedures or environment that has the potential to affect the aseptic process or an addition of new product containers or container-closure combinations

15- Revalidation



- All APS runs should be fully documented and include a reconciliation of units processed (such as units filled, incubated and not incubated).
- The justification for filled and non-incubated units should be included in the documentation.
- All interventions performed during the APS should be recorded, including the start and end time of each intervention and the involved person.
- All microbial monitoring data, as well as other testing data, should be recorded in the APS batch record

16-General Notes



- ❑ <u>Liquid Products</u>

- Vial Products

The liquid growth medium for the simulation test is prepared and kept in a sterile holding vessel for the maximum permitted holding time before starting the simulation test. If the bulk solution is stored under refrigerated conditions during the holding time then this should also be performed for the medium. Vials and closures should be prepared as in regular production.

- Suspension Products

This procedure is comparable to the filling of liquid products, except for the process step of maintaining suspension of the ingredients. The stirring or recirculation should be part of the simulation. If aseptic additions are made to the bulk solution these should be simulated by the use of inert sterile liquids/powders.

16-General Notes



Ampoule Products

- Open or closed ampoule types may be used.
- They should be sterilised by dry heat and afterwards used in the simulation test as per the regular production run.
- Ampoules should be prepared as in regular production.

Injectable Powder Products

There are two possibilities for simulation of this process.

- Either by filling a sterilized liquid growth medium into the sterile container or adding a powder (inert or growth medium) before or after a sterile diluent (WFI or growth medium).

Inert materials commonly used include: polyethylene glycol 8000 and carboxymethyl cellulose. These materials are usually sterilized by irradiation.

16-General Notes



❑ Semi-Solid Products (e.g. sterile ointments)

- For this simulation test the liquid growth medium is thickened to the appropriate viscosity, used as in the routine production procedure.
- Suitable thickening agents are agar and carboxymethyl cellulose.
- Metal and plastic ointment tubes prevent the examination of the medium in-situ.

✓ Usually the whole content of the tube should be examined and this is usually achieved by squeezing the contents into a plate (petri dish), and after whirling it is examined for turbidity and fungal colonies under defined light conditions or by performing a sterility test.

✓ If properly validated, an alternative method for detection of contamination of semi-solid products could be the use of media which changes colour in the presence of contamination.

✓ Alternatively, special tubes which do not contain the opacifying agent may be purchased for the process simulation.

16-General Notes



- Ear and eye drops are typically marketed in plastic containers.

- Containers, inserts, closures and where applicable over seals are washed and sterilized as in regular production.
- Instead of sterilization with heat, irradiation or ethylene oxide are used
- Whilst clear plastic containers are frequently used for process simulation trials, the plastic is usually slightly opaque and thus hinders identification of contaminated units that show only a slight haze.
- In such case examination under natural or room lighting would not suffice.
- Where opaque containers are used for process simulation trials the whole contents should be removed for examination.

17-Media Fills – Typical Inspection Concerns





- Inadequate investigation of media fill failure
- Inadequate training of employees after media fill failure
- Media fills did not follow required SOP
- Media fill aborted due to high particulate counts, but inadequate investigation into reasons for high counts
- Defective vials discarded prior to incubation and not counted as failures
- Number of units filled too small
- Media fills did not simulate what was documented in MF-validation specific batch records
- Certain environmental data not collected during fill.

17-Media Fills –Inspection Concerns



- There was no clear history for previous performed media fills
- There was no evidence of usage clear bottles in media fill
- It was mentioned to cool media fill till 25-30°C without mentioning the way to monitoring temperature.
- Chart of sterilization of tools &primary packs were not attached..
- Codes of autoclave LAF, storage LAF, and the capacity of receiving tank were not mentioned.
- The inversion of bottles and incubation stage were not timed or dated in batch record
- Simulation of media fill wasn't assured as The filtration of bulk solution was done for one receiving tank although filtration process was done through the two receiving tanks in routine work
- Environmental monitoring is recorded only once through all the time of media fill
- There was no challenge for the maximum holding time of sterilization of machine parts and gowns..



17-Media Fills – Typical Inspection Concerns



The unsatisfactory part of media fill simulation is this:

– There are lots of reasons why unsafe aseptic processes could still give perfect media fill results (zero contaminants)

- Media does not support growth
- Media Fill done in "best conditions" which do not reflect reality
- Routine risks omitted (accidentally or intended)

– The only way media fills give us any useful information about our aseptic processes is when they fail, we investigate, we find a fault in the process, and then we fix the faults



Thank you


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CPD
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PROFESSIONAL DEVELOPMENT
مركز التطوير المهني المستمر

Dec 2023





Cleaning Validation

Presented by:
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Content

1. Cleaning
2. Cleaning methods & mechanisms
3. Cleaning Validation

Cleaning



Definition:

The process of removing potential contaminants from process, equipment and maintaining the condition of equipment such that the equipment can be safely used for subsequent product manufacture.

Why we clean?



- Patient Safety
- Product integrity
  - Cross-contamination
  - Microbial integrity
  - Lot integrity
- Equipment reuse
- Regulatory compliance

What we clean?



Pharmaceutical products can be contaminated by a variety of substances such as contaminants associated with:

- **Microbes** (cleaning should remove endotoxins, bacteria, toxic elements, and contaminating proteins).
- **Previous products** (both active pharmaceutical ingredients APIs and excipients or their decomposition residues).
- Residues of **cleaning agents** or their decomposition.
- **Airborne materials**, such as dust and particulate matter.
- **Lubricants** and ancillary material, such as disinfectants.

How we clean?



- Cleaning Validation master plan / policy.
- Involves "intersection" of two products

– Product (A) just manufactured (Efficient cleaning to remove residues to acceptable level).

– Product (B) subsequently manufactured (residue levels based on possible contamination of this product).

- Must always evaluate effects on subsequently manufactured product.

How we clean?



- Written general procedures for cleaning (SOPs) should be issued detailing the cleaning processes used for various pieces of equipment.

- SOP should clarify the responsible for performing and approving the cleaning action.

- Dedicated equipment should be used for **products** which are difficult to clean, **equipment** which are difficult to clean, products with **high safety risk** where it is not possible to achieve the required cleaning acceptance limits using a validated cleaning procedures.

Cleaning validation



Cleaning validation is a documented evidence with a high degree of assurance that one can consistently and effectively clean a system or equipment to predetermined and acceptable limits.



- Validation data should verify that the cleaning process will reduce the specific residues to an **acceptable level**. However, it may not be possible to remove absolutely every trace of material, even with a reasonable number of cleaning cycles.

- The permissible residue level, generally expressed in **parts per million (ppm),** should be justified by the manufacturer.

Cleaning methods



1. <u>Clean in place (CIP)</u>

   Clean in place is an automated system that consists of a recirculation system that uses various tanks and return system such as return pump. Equipment cleaning is performed in place without disassembly.

2. <u>Clean out of place (COP)</u>

   Clean-out-of-place equipment includes such items as wash tanks used to clean small parts or parts removed from large equipment.

3. <u>Manual cleaning</u>

   The manual cleaning method is accomplished by scrubbing, brushing and/or wiping by the operator.

Cleaning methods



Item	Manual cleaning	Automated cleaning
Responsibility	- Trained staff - Rely on the details of cleaning procedures (SOP).	- Automated processes - Rely on automated or semi automated system. - Instruments control for reproducibility.
Monitoring	- Few effective means of monitoring unless periodic sampling.	- Monitoring is performed through instrumentation. - Calibration of sensors & system validation is must.
Qualification	- No requirement for IQ/ OQ of the cleaning process	- Requirement for IQ / OQ of instruments & controls is must.

CIP



Process Vessel

Detergent

Water

CIP Pump

Scavenge Pump

Drain

Key elements to be considered in design (Cont.)



- **Levels of cleaning:**

- Level one: (Minor cleaning)

This is used between manufacturing of different batches of the same product.

- Level two: (Major cleaning)

This is used between manufacturing of different Batches of different product

and / or at the end of manufacturing campaign.

Cleaning mechanism



- **Mechanical actions** (refer to physical actions i.e. scrubbing, brushing, using pressured water to remove particulates).

- **Dissolution** by dissolving residues using suitable solvents e.g:

  - Water (the most common, non –toxic solvent, cheap, doesn't leave residues, and environment friendly).

  - In some cases it may be preferable to use non aqueous solvent or a combination of aqueous & non aqueous solvents acc. To the solubility characteristics of the material.

  - Alkaline or acidic solvents can enhance dissolution of the materials.

Cleaning mechanism



- **Detergency** (by using surfactants, usually in aqueous system).
- Detergents act in four different ways:

  - Wetting agents,

  - Solubilizers;

  - Emulsifiers, and

  - Dispersants.

- **Chemical reactions** (Such as oxidation and hydrolysis in which the residues are chemically changed e.g. Sodium Hypochloride).

Three stages of cleaning validation



1: Design (includes development)

2: Qualification (protocols & reports)

3: Continued process verification (validation maintenance, ongoing process verification, ongoing process control)

Aspects to be considered in the selection of cleaning agent



- Safety
- Toxicity
- Stability
- Easily to be prepared.
- Rinsing (Easily to be rinsed).
- Compatibility (not interacted with materials of equipment e.g. rubber, silicone,SS..etc).
- Availability.
- Supplier qualification.

Cleaning agents



1. **Water**

2. **Solvent:** includes organic solvents such as acetone, ethanol, and ethyl acetate.

3. **Commodity chemicals:** which include inorganic chemicals such as sodium hydroxide and phosphoric acid.

4. **Formulated cleaning agents:** It is the largest class of cleaners. It may include surfactants (sod lauryl sulphate), sequestrant.

Key elements to be considered in design



- **Equipment to be cleaned** (material of construction & difficult locations to be cleaned).

- **Soils to be removed** (API or excipients, fresh or dried during process, amount of soil).

- **Cleaning agents**.

- **Cleaning methods** (Extent of automation or Extent of disassembly e.g. CIP, Parts washer or Manual, Clean individually or as train).

- **Cleaning parameters** (**Time**, Cleaning chemistry, Concentration, **Temperature**, Water quality (purified or WFI) & Rinsing cycles.

Key elements to be considered in design (Cont.)



- Time limitation:

1. Clean holding time (CHT): The Max. time that equipment kept clean after cleaning process. (Microbiologically)

2. Dirty holding time: The time between the end of production and the cleaning of the equipment

3. Time between the cleaning and drying process: This limitation will control the microbial contamination (bioburden)

4. Campaign length (batches/ days)

Elements of cleaning validation



1. **Worst case determination**
2. Establishment of acceptance criteria
3. Sampling procedure
4. Analytical method and its validation
5. Validation protocol
6. Validation report

1. Worst case determination



<u>**Criteria to be considered during worst case determination**</u>

- <u>Solubility</u>: “Least Soluble” the main factor.

- <u>Potency:</u> “Most Potent” a second factor often utilized in the selection of "worst case" products. They are those products which are the most potent [on a weight basis], and therefore have the lowest numerical level for acceptable residue.

- <u>Hardest to Clean “cleanability”:</u> a subjective selection based upon operational experience with the various formulations. This product may by virtue of its formulation or method of manufacture appear to be more difficult to clean based upon some criteria.

- Highest toxicity (LD50)/ lowest PDE

1. Worst case determination



- Solubility: Solubility of active in water/solvent/ cleaning agent being used to clean equipment
- Example:

Solubility (From USP)	Solubility Factor
Very Soluble	1
Freely Soluble	2
Soluble	3
Sparingly Soluble	4
Slightly Soluble	5
V. Slightly Soluble	6
Practically Insoluble	7

1. Worst case determination



– Potency: potency of products based on normal daily dose of products

- Example:

Normal Daily Dose	Potency Factor
< 5mg	5
5 – 199 mg	4
200 – 400 mg	3
400 – 600 mg	2
600 – 800 mg	1

1. Worst case determination



- Batch size of Next Product: Lowest batch size ,more worse the situation
- Strength: Highest strength of previous product ,more worse the situation
- Maximum daily dose of next product: Highest the number of daily dose ,more worse the situation
- Common equipment surface area: Largest common surface area of equipment, more worse the situation

1. Worst case determination



- "Bracketing by product" should be done only when the products concerned are similar in nature or property or same substance in different strength, and will be processed using the same equipment.
- Identical cleaning procedures should then be used for these products. When a representative product is chosen, it should be the one that is most difficult to clean (worst case).
- The grouping is usually based on the formulation or the dosage form of the product.
- "Bracketing by equipment" should be done only when it is similar equipment, or the same equipment in different sizes (e.g. 300-l, 500-l and 1000-l tanks).

2. Establishment of acceptance criteria



Determination of acceptance criteria:

A. **Physical determination**
B. Chemical determination
C. Microbiological determination

A. Physical determination



- There should be **no** residue from the previous product, from reaction by products or degrades, or from the cleaning process itself (e.g. detergents or solvents).

- Visible residue limit (4µg/ cm^2)

- Special attention should be given to areas that are hard to clean (e.g. agitator shafts, thermo wells, discharge valves etc.) and areas that would be difficult to verify on a routine basis.

A. Physical determination



Procedure for spiking study

- In order to determine the visual limit of detection with high reliability, the test conditions were matched as far as possible with the conditions later to be met during the practical execution of the cleaning validation.

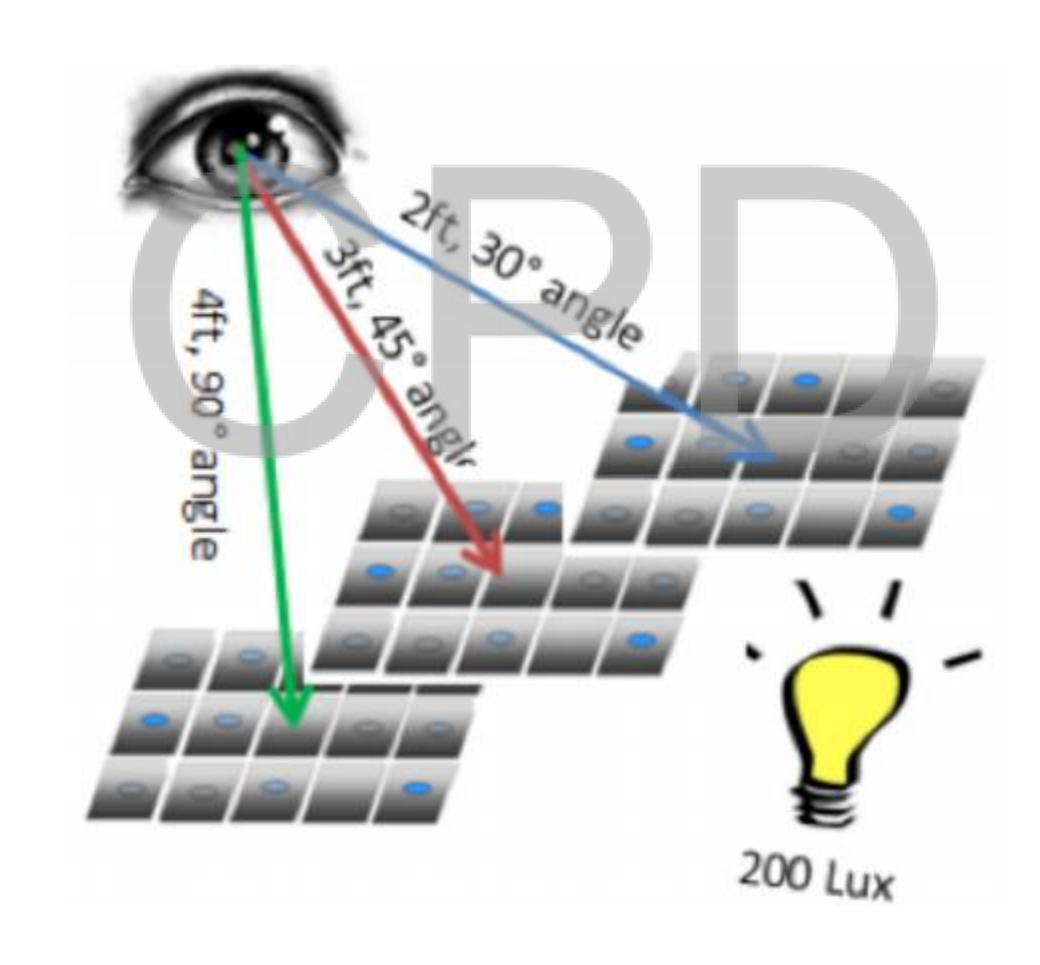
Procedure:

- Surface properties (the same surface roughness as the machine surface).
- Same lighting as in the production department
- Test execution (eye distance to the surface and the duration of observation) were the same while examining the machine surface.
- Distribution of active pharmaceutical ingredient on the surface (even film distributed on the entire area).
  - Serial dilutions of standard were prepared and a defined volume of 1 ml from each dilution was applied on a marked test surface
  - Once the solvent was fully evaporated, the visual limit of detection was determined by comparing the individual tested areas.

A. Physical determination

Spiking study

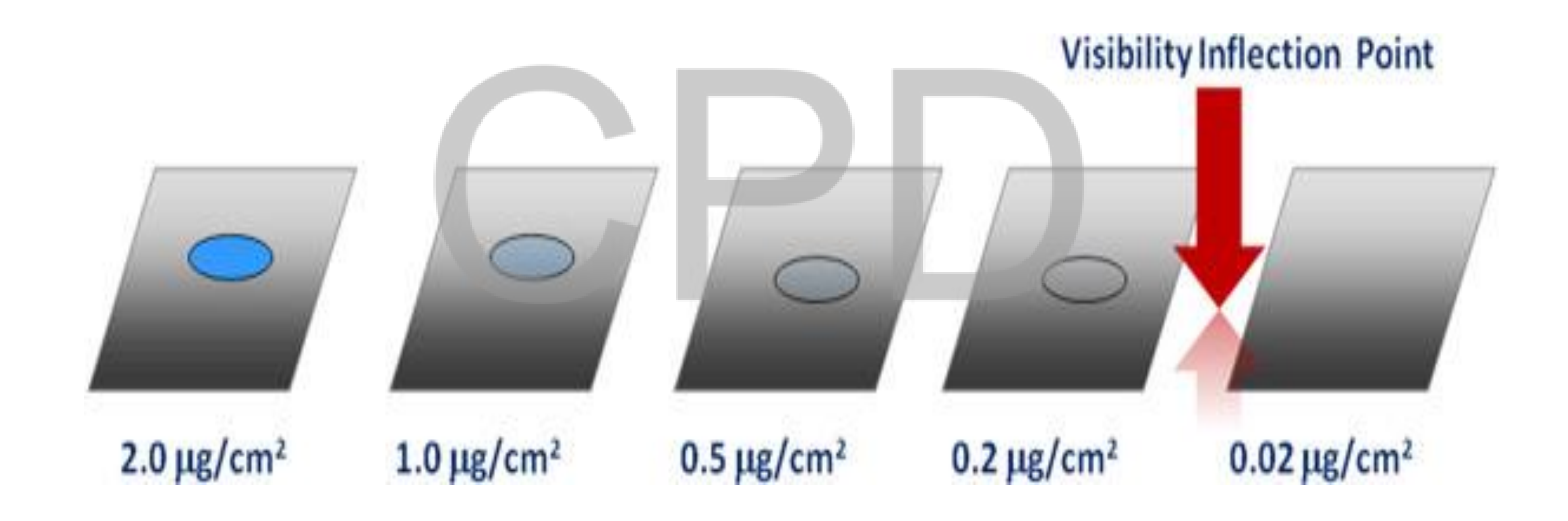




A. Physical determination

Spiking study





2. Establishment of acceptance criteria



Determination of acceptance criteria:

A. Physical determination
B. Chemical determination
C. Microbiological determination

B. Chemical determination



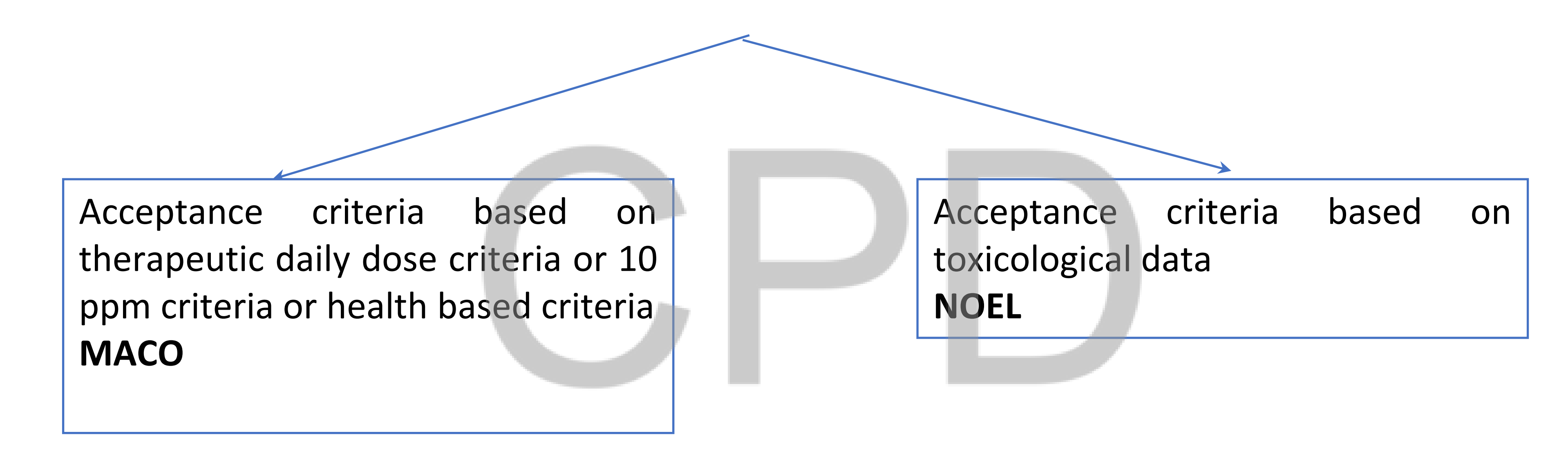
- The acceptance criteria established for contaminant levels in the sample should be **practical, achievable and verifiable.** The rationale for the residue limits established should be **logical,** and based on the knowledge of the materials involved.

- No more than 10 ppm of one product will appear in another product

- No more than 0.1% of the normal therapeutic dose of one product will appear in the maximum daily dose of a subsequent product.

B. Chemical determination





Max. allowable carryover (MACO): The quantity of compounds permitted to carry-over in subsequent product without any adverse effect to the product or patient.

B. Chemical determination



Therapeutic daily dose approach (Dose criterion):

This method only applied when the therapeutic daily dose is known. Generally used for final products.

Maximum allowable carryover (MACO) calculation:

$$MACO = \frac{TDD \times MBS \times SF}{LDD}$$

Where,

- MACO is the maximum allowable carryover.
- TDD is the minimum therapeutic daily dose of the previous product.
- LDD is the Maximum therapeutic daily dose of the next product.
- MBS is the Minimum batch size of the next product.
- SF is the safety factor(1/100 for topical, 1/1000 for oral products, 1/1000 for parenteral).

B. Chemical determination



- **Acceptance criteria based on 10 ppm criterion**:

$$MACO = \frac{10 \ X \ MBS}{1000000}$$

- **PDE approach limit (New):**

$$MACO_{PDE} = \frac{PDE \ X \ MBS}{LDD}$$

B. Chemical determination



- Health based exposure limit (New approach)

- Permitted daily exposure (PDE): Represents a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime.

B. Chemical determination



- **Allowed daily amount**

- This has been called the Acceptable Daily Intake (ADI), Acceptable Daily Exposure (ADE), Permitted Daily Exposure (PDE), Safe Daily Intake (SDI)
- It is based on a safety/toxicity evaluation
- An ADI/ADE/PDE value based on toxicity information

B. Chemical determination



- Procedure:

Calculate the ADE (Acceptable Daily Exposure) or PDE (Permitted Daily Exposure) according to the following equations and use either result for the calculation of the MACO.

$$ADE = \frac{NOAEL \times BW}{UFc \times MF \times PK}$$

$$PDE = \frac{NOAEL \times BW}{F1 \times F2 \times F3 \times F4 \times F5}$$

NOAEL: No Observed Adverse Effect Level (mg/kg/day)

BW: Is the weight of an average adult (e.g. 70 kg)

Ufc: Composite Uncertainty Factor: combination of factors which reflects the interindividual variability, interspecies differences, sub-chronic-to-chronic extrapolation, LOEL-to-NOEL extrapolation, database completeness.

MF: Modifying Factor: a factor to address uncertainties not covered by the other factors

PK: Pharmacokinetic Adjustments

F1-F5 : Adjustment factors to account for uncertainties. Refer to EMA Guidance 2 for further explanation.

B. Chemical determination



Acceptance criteria based on toxicological data

In cases in which a therapeutic dose is not known (as for intermediates or for detergents), toxicity data may be used for calculating acceptance criteria.

$$\text{NOEL} = \frac{LD_{50}\ (\text{g/kg}) \times 70\ (\text{kg person})}{2000}$$

Where,

- **NOEL** = No observable effect level
- **LD_{50}** = Lethal dose 50 in g/kg anima.l The identification of the animal (mouse, rat etc.) and the way of entry (IV, oral etc.) is important (mg/kg)
- **70 kg =** Average adult weight
- **2000** = 2000 is an empirical constant

$$\text{MACO} = \frac{\text{NOEL} \times \text{MBS}}{\text{LDD}_{\text{next}}}$$

B. Chemical determination



- The most astringent MACO is used to calculate the acceptance limit of each sample.
- $$\text{MACO sample} = \frac{\text{MACO calculated } (\mu g)}{\text{Shared equipment surface area } (cm^2)}$$

2. Establishment of acceptance criteria



Determination of acceptance criteria:

A. Physical determination
B. Chemical determination
C. **Microbiological determination**

C. Microbiological determination



- The main issue is that merely one organism in the equipment could possibly result in a significantly higher contamination level in the product manufactured in that equipment.

- The swab/rinse sampling of selected areas of the equipment train will be performed in order to determine the number of colony forming units (CFUs) present.
- Acceptance criteria of microbiology:

- Absence of fungi.
- Number of cfu depends on which class & usually sample area is 5 x 5 = 25 cm^2 is chosen for direct surface sampling.
- Endotoxin limit (for sterile)

C. Microbiological determination



- For production areas using purified water in manufacturing and final rinse, PW limit is considered the acceptance criteria for microbiology (100CFU/ml).

- For production areas using WFI in manufacturing and final rinse, WFI limit is considered the acceptance criteria for microbiology (10 CFU/100 ml).

- Equipment should be stored in a dry condition after cleaning. Stagnant water should not be allowed.

- There should be documented evidence to indicate that routine cleaning and storage of equipment does not allow microbial growth.

Elements of cleaning validation



1. Worst case determination
2. Establishment of acceptance criteria
3. **Sampling procedure**
4. Analytical method and its validation
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3. Sampling procedures



- Equipment should normally be cleaned as soon as possible after use. This may be especially important for operations with topical products, suspensions and bulk drug or where the drying of residues will directly affect the efficiency of a cleaning procedure.

- Two methods of sampling are considered to be acceptable. These are direct method **(surface sampling)** and indirect method (**rinse samples)**. A combination of the two methods is generally the most desirable.

- The practice of re-sampling should **not** be used before or during cleaning and operating and is acceptable only in rare cases.

A. Direct surface sampling (Swab sampling)



The type of sampling material used and its potential impact on the test data is important as the sampling material may interfere with the test. (For example, the adhesive used in swabs has been found to interfere with the analysis of samples).





A. Direct surface sampling (Swab sampling)

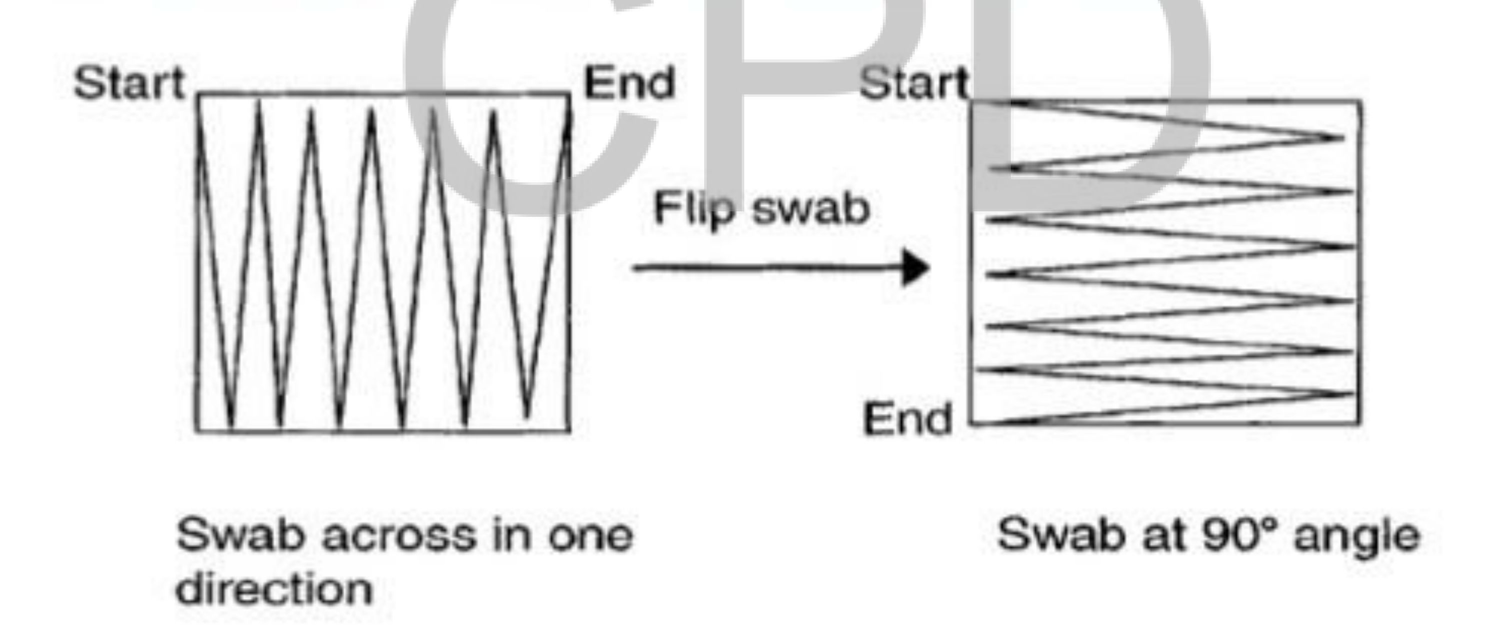


Factors that should be considered include:

- The supplier of the swab
- area swabbed
- number of swabs used (reasonable to machine surface area).
- whether they are wet or dry swabs
- swab handling and swabbing technique.
- The location from which the sample is taken should take into consideration the composition of the equipment (e.g. glass or steel) and the location (e.g. blades, tank walls or fittings).
- Worst case locations should be considered. The protocol should identify the sampling locations.
- Critical areas, i.e. those hardest to clean, should be identified
- The sampling medium and solvent used should be appropriate to the task.

A. Direct surface sampling (Swab sampling)





❖ **Swab sampling techniques:**

(11) Wiping should be **unidirectional** at a time. **Parallel strokes** should be employed to cover entire swab area.

Swab recovery study



- It is used to define how capable the selected sampling method is of recovering the drug substance from the clean surfaces, and how capable the analytical method is of identifying the drug substance accurately and reliably in combination with the sampling method.

- Recovery factor is usually determined by spiking known amounts of the expected residue on surfaces of the same material (e.g., stainless steel, glass, plastics) as the equipment to be sampled.
- Recovery percentage from surface= $\frac{\text{Amount detected}}{\text{Amount spiked}} \times 100$

Recovery factor



Recovery

> 80% is considered good

> 50% is considered reasonable

< 50% is considered questionable

B. Indirect surface sampling (Rinse sampling)



- This method allows sampling a large surface of areas that are inaccessible or that cannot be routinely disassembled and provides an overall picture.

- Rinse samples may give sufficient evidence of adequate cleaning where accessibility of equipment parts can preclude direct surface sampling, and may be useful for checking for residues of cleaning agents, e.g. detergents.

B. Indirect surface sampling (Rinse sampling)



- This method is based on the analytical determination of a sample of the final rinsing solvent (generally water) used in the cleaning procedure.

- It is important to ensure that the chosen solvent has appropriate recovery of residues being quantified.

- Rinse samples should be used in combination with other sampling methods such as surface sampling.

Notes



- Sampling for estimation of clean holding time microbiologically is may be done **daily or at the end of the period to be validated.**

- Sampling for estimation of dirty holding time is done by letting the equipment dirty for 48 hours then clean, the acceptance limit should be passed. (API residue – microbial residue – detergent residue).

- Blank sample of water use point used in cleaning the equipment is kept to be a reference in case of failure of rinse results.

- Sampling of rinse analysis should be collected from the final rinse.

Notes (Cont.)



- Microbiology sampling should be done before chemical sampling to avoid contamination.
- Collecting rinse samples should be done before application of alc. To avoid increase oxidizable substances.
- Only one sample should be collected from each sampling point.

Elements of cleaning validation



1. Worst case determination
2. Establishment of acceptance criteria
3. Sampling procedure
4. **Analytical method and its validation**
5. Validation protocol
6. Validation report

4. Analytical method & its validation



- The analytical methods should be validated before the cleaning validation study is carried out.

- The analytical methods used to detect residuals or contaminants should be specific for the substance to be assayed and provide a sensitivity that reflects the level of cleanliness determined to be acceptable by the company.

- The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminants and preferably to be lower than acceptance limit by 25%.

4. Analytical method & its validation



- **Validation of the analytical method should include:**
- Precision, linearity, Accuracy and Specificity
- Limit of detection (LOD)
- Limit of quantitation (LOQ)
- Recovery by spiking with the analyte
- Reproducibility

4. Analytical method & its validation



Specific analytical methods:

- HPLC
- UV Spectrophotometry
- Atomic absorption
- Capillary electrophoresis
- ELISA

4. Analytical method & its validation

<u>**Non specific analytical methods include:**</u>

Total organic carbon:

- This nonspecific method can be used to test for residues of previously manufactured products, cleaning detergents, chemicals, solvents, by-products, degrades, and microbial contaminants.

Conductivity measurement:

- Conductivity is strongly sensitive to any ionic or soluble inorganic contaminant present.

4. Analytical method & its validation



pH measurement:

- Major advantages of this direct method is that no sampling processing is necessary and that readings can be obtained directly by inserting a pH probe into the sample solution.

- Since many commercial cleaning agents have strongly acidic or basic character, this simple measurement is an additional piece of evidence that the cleaning agent has been removed following the cleaning procedure.

Elements of cleaning validation



1. Worst case determination
2. Establishment of acceptance criteria
3. Sampling procedure
4. Analytical method and its validation
5. **Validation protocol**
6. Validation report

5. Validation protocol



- The objectives of the validation process.
- The scope of the validation (Production line).
- The people responsible for performing and approving the validation study.

- <u>Production</u>

 - Production manager arrange for training of the operators responsible for conducting the cleaning process without deviations & record this training in training records reviewing of validation protocol.

 - Production manager review the qualification & protocol.

 - Production department for issuing cleaning process & procedures.

 - Give information about the difficulty of cleanability.

5. Validation protocol



- Quality control

  - Determination of method of analysis.

  - Qc manager takes the decision of the analytical results.

  - Qc analyst responsible for analysis of the samples according to the validated methods of analysis & record data. (Chemical & microbiological).

  - QC supervisor reviews the analysis results & checks the raw data. (Chemical & microbiological).

  - Issuing the analysis report.

  - Writing the deviation report if present.

5. Validation protocol



- Quality Assurance:

- Prepare & review the cleaning validation protocol.
- Prepare & review the cleaning validation report.
- Determination of the sampling location.
- Issuing the sampling plan.
- Sampling acc. To the plan incorporation with the IPC staff.
- Investigate with other related departments if any deviation has occurred.
- Writing deviation report if present.
- QA manger review & approve the cleaning validation protocol.
- Determination of the acceptance criteria through calculating the score of each product to determine the worst case selection.
- Photographs the equipment & determine with the production department the sampling points of swabs and rinse.

5. Validation protocol



- the description of the equipment to be used, including a list of the equipment, make, model, serial number or other unique code.

- The interval between the end of production and the commencement of the cleaning procedure (interval may be part of the validation challenge study itself).

- The maximum period that equipment may be left dirty before being cleaned as well as the establishment of the time that should elapse after cleaning and before use.

- The cleaning procedures (documented in an existing SOP, including definition of any automated process) to be used for each product, each manufacturing system or each piece of equipment.

5. Validation protocol



- All the instruments used for routine monitoring, e.g. conductivity meters, pH meters and total organic carbon analyzers.
- The number of cleaning cycles to be performed consecutively (Three consecutive runs).
- The sampling procedures to be used (direct sampling, rinse sampling, in process monitoring and sampling locations) and the rationale for their use.
- The data on recovery studies (efficiency of the recovery of the sampling technique should be established).
- The analytical methods (specificity and sensitivity) including the limit of detection and the limit of quantification.
- The acceptance criteria (with rationale for setting the specific limits) including a margin for error and for sampling efficiency.

5. Validation Report



- The relevant cleaning records (signed by the operator, checked by production and reviewed by quality assurance).
- The results of the cleaning validation should be presented in cleaning validation reports.
- Conclusions regarding the acceptability of the results, and the status of the procedures being validated.
- Any recommendations based on the results or relevant information obtained during the study including revalidation practices if applicable.
- Review of any deviations from the protocol.
- Signatures of those who approve the report.
- references

Change control & Revalidation



- Validated cleaning process should be subject to change control.
- Changes include unplanned and planned changes. The key to change control is to evaluate the effect of any change, correct the changed item if possible, implement any increased monitoring as needed, and document the procedure.
- In some cases it may be necessary to make revalidation.

Revalidation

- At some point it may be necessary to revalidate all processes, equipment, and people.
- This revalidation is performed to determine whether the original validation still applicable to the cleaning process as it is now performed or not.

Change control & Revalidation



- <u>Cases of required revalidation</u>:

- Introducing a new product and considered a worst case.
- Change in processing equipment.
- Change in cleaning procedures.
- Change in the cleaning equipment.
- Change in cleaning agent.

Cleaning verification



- Verification of cleaning by repeat testing which give a clear image that cleaning method and procedures are adequately performed to remove the residuals to the acceptable limits.

- Cleaning procedures should by periodically reviewed **every 2-3 years.**

- SOP also should be reviewed.



SUMMARY

Questions



References



- ACTIVE PHARMACEUTICAL INGREDIENTS COMMITTEE (APIC): Guidance on aspects of cleaning validation in active pharmaceutical ingredients.
- WHO TRS 1019 annex 3, Good manufacturing practices: Guidelines on validation, appendix 3, cleaning validation.
- PDA technical report no. 29 Points to consider in cleaning validation.



Thank you

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Professional Development
مركز التطوير المهني المستمر





Validation of Computerized Systems

Presented by:
Ph. Mohamed Salah
GMP lead Inspector

Content

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Content

5 FDA Warning Letter Examples

6 **Attachments**

7 references

INTRODUCTION



- The FDA requires that these computer systems, an integral component of research and development, manufacturing, distribution, sales and marketing, must be properly developed, tested and used according to the formal quality standards.

- To establish the evidence and the associated documentation that a system meets these standards and that it will continue to do so over the time, requires Computer System Validation.

Objectives



To discuss validation of computerized systems including:

- System specifications
- Functional specifications
- Security
- Back-ups
- Validation:
  - *Hardware*
  - *Software*

– Production and quality control.

GENERAL



- Computer systems used in planning, specification, programming, testing, commissioning, document operation, monitoring and modifying.
- Validation: Evidence and confidence
  - *intended use, accuracy, consistency and reliability.*
- ➢ Both the system specifications and functional specifications should be validated.
- Periodic (or continuous) evaluation should be performed after the initial validation.

- **Written procedures for:**

performance monitoring, change control, programme and data security, calibration and maintenance, personnel training, emergency recovery and periodic re-evaluation

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Step 2: Define Requirements



Intended application

Intended environment

Computer environment

Laboratory

User requirements

Operating systems

Networks

Compatibility with other systems

Functions to perform applications

Functions to comply with regulations
(Annex 11, Part11)

Verify with the vendor if requirements are met

Step 3: Qualify the Suppler



1. Purpose: determine the adequacy of the suppliers quality system
2. Types of assessment
   - Preliminary assessment (questionnaire, postal audit)
   - Detailed on-site audit (quality system, process, product)
3. Extent of the assessment depends on
   - criticality of the system, complexity
   - risk to data integrity associated with use of the system
   - ability to verify system functionality in the lab
4. **Can reduce in-house testing through tests done by the supplier**

Document Vendor Selection



Requirements	Results	Passed
1) Company		□ yes □ no
Experience with the vendor		□ yes □ no
Recognition in the market place		
2) Quality Assurance		
ISO Certification		□ yes □ no
Documented software development		□ yes □ no
3) Product functions (provide detailed list)		□ yes □ no
4) Services and Support		
Provide specifications list		□ yes □ no
Installation service		□ yes □ no
IQ/OQ services		□ yes □ no
Phone and onsite support		□ yes □ no

Supplier Contributions for Validation



- Operate product development, manufacturing and support in a documented quality management system
- Document software development and validation activities
- Summarize testing activities for hardware and software
- Provide conformity declarations and/or validation certificates for equipment and software
- Respond to supplier assessment requirements in timely manner
- Allow and be cooperative with vendor audits
- Allow access to test conditions and results
- Offer IQ/OQ services
- Provide software for system suitability testing

Documents that Should be Provided by Software Suppliers

- Functional specifications
- Documented evidence of working under a recognized quality system (ISO 9001 or equivalent)
- Validation certificate or declaration of system validation
- Description of software development and validation process
- Site preparation checklist
- Documented evidence of qualifications for personnel that develop and support computer systems
- Declaration of conformity to specifications for equipment hardware

Step 4: Perform and Document Installation Qualification

- Collect supplier’s environmental conditions, operating and working instructions and maintenance requirements
- Compare systems, as received, with purchase order
- Install of systems according to vendor specifications
- Make system drawings (e.g., data flow)
- Check documentation for accuracy and completeness
- Document all components with asset and serial numbers

Conduct Risk Management



- Should be applied **throughout the lifecycle** of a computerized system
- Decisions on extent of validation and data integrity controls should be based on a justified and documented risk assessment
  - Impact on product quality and patient safety
  - Impact on data integrity

Step 5: Test for Operational Qualification



- Identify critical functions for the computer systems as defined in functional and user requirement specifications
- Develop test cases for the functions and define acceptance criteria
- Perform the tests
- Evaluate results and compare with acceptance criteria
- Document results

Validation of hardware



- **Appropriate tests and challenges to the hardware**
- **No influence of static, dust, power-feed voltage fluctuations and electromagnetic interference**
- **Hardware is considered to be equipment**
  - *focus on location, maintenance and calibration as part of the Qualification*

- It should prove:
  - ❖ **Appropriate capacity**
  - ❖ **Operational limits**

    e.g. memory, connector ports, input ports
  - ❖ **Performance under worst-case conditions**

    e.g. long hours, temperature extremes
  - ❖ **Reproducibility/consistency**

    e.g. by performing at least three runs under different conditions

Validation of hardware (2)



- Written qualification protocols; results in qualification reports kept
- Revalidation – in case of significant changes
- Validation may be performed by the vendor – but ultimate responsibility remains with the company
- If records kept by supplier, manufacturer still has to have sufficient records to allow assessment of the adequacy of the validation

Validation of Software



- The term used to describe the complete set of programmes used by a computer, and which should be listed in a menu
- Records are considered as software
- Focus should be placed on:
  - accuracy, security, access, retention of records, review, double checks, documentation and accuracy of reproduction

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Validation of Software (3)



- **Points to be considered may include:**

  Function: Matching the assigned operational function (e.g. generate batch documentation, different batches of material used in a batch listed)

  Worst case: Validation under different conditions (e.g. speed, data volume, frequency)

  Repeats: Sufficient number of times (e.g. replicate data entries)

  Documentation: Protocols and reports

  Revalidation: In case of significant changes made

What to Test



- Functions that can be impacted by the user's environment
  - User configurations
  - User customizations
  - Hardware configurations, cabling (communication between computer and equipment)
- Real critical system functions
- Run well characterized test sample
  - Compare test results with acceptance criteria

Step 6: Ensure Ongoing Performance (PQ)



System Testing

- Regular system performance tests
  - System suitability testing
  - Development, review, approval of SOPs

Maintenance

- Regular disk maintenance
- Regular virus checks
- Environmental control

Regular data back-up

Change control procedures and logs



Step 7: Implement Change Control System



Main reasons for changes: hardware maintenance and repair and software upgrades
Changes must follow a documented change procedure
Procedure should require risk analysis and evaluation if the change may affect the computerized system's validation status
Document changes; what, why, who, how tested?

Step 8: Write the Validation Report



- Should include brief description of each major project activity
- Used to review all preceding validation
  activities and indicate status of the system prior to implementation into a production or any area
- Deviations from the project plan should be documented and risk assessment should be performed

Risk assessment for deviations

- Approval of the validation report pre-requisite for release

Validation Phases – 4Q Model

APPROACH FOR EXISTING EQUIPMENT

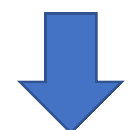


Define system use



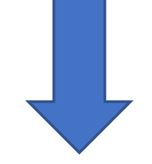
- **Document equipment use**
- **Document applications**
- **Document used functions**

Installation Qualification



- Enter all modules and systems in a database
- Hardware, Firmware, Software

Operational Qualification



- Document past tests
- Test of functional specifications
- Test of performance functions

Performance Qualification

- System test (system suitability testing)
- Preventive maintenance

Validation Report

FDA Warning Letter/483/EIR



- During the inspection, I asked if the computer software has been validated. **I was told that the software was validated by the manufacturer**.
- The managing director provided me a copy of the letter the received from (the vendor). **The letter indicated that the software was validated**.
- I told the managing director **I still need to see what they have done to validate the system** since the computer was making a decision to accept or reject potential donors.

No validation at user's site

Validate computer systems at the user’s site

FDA Warning Letter/483/EIR



- Failure to adequately validate computer software used in an automated process for its intended use according to an established protocol
- For example, no person from your firm reviewed or approved the third party approval test results for the original Complaint System Validation" used in your firm's quality system.

3rd party validation results not reviewed

User firm should always review validation results

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FDA Warning Letter/483/EIR (2012)



User access levels for the software were not established and documented. Currently, laboratory personnel use a common password to gain access to the system and there are no user access level restrictions for deleting or modifying data.

Group Rather than individual passwords

Assign unique user ID for each person

FDA Warning Letter/483/EIR



- User access levels for the [redacted] software were not established and documented. Currently, laboratory personnel use a common password to gain access to the system and there are no user access level restrictions for deleting or modifying data. (W-198)

Group Rather than individual passwords

Assign unique user ID for each person

FDA Warning Letter/483/EIR



Data security protocols are not established that describe the user's roles and responsibilities in terms of **privileges to access, change, modify, create, and delete projects and data** (242)

Roles and Responsibilities not Established

Develop a list with roles and responsibilities for functions
Implement and validate the procedures

FDA Warning Letter/483/EIR



- Your firm's review of laboratory data **does not include a review of an audit trail** or revision history to determine if unapproved changes have been made.. (229)
- **Deviation**: Missing Review of Audit Trail
- **Root cause** (assumed for the purpose of this case study):
  No procedure for formally review electronic audit trail
- **Corrective action** to correct the existing violation
  Develop and implement procedure for reviewing e-audit trail by QA
- **Preventive actions**
  Apply procedure to other computer systems that record e-audit trail.

Electronic audit trail not reviewed

Data Checks

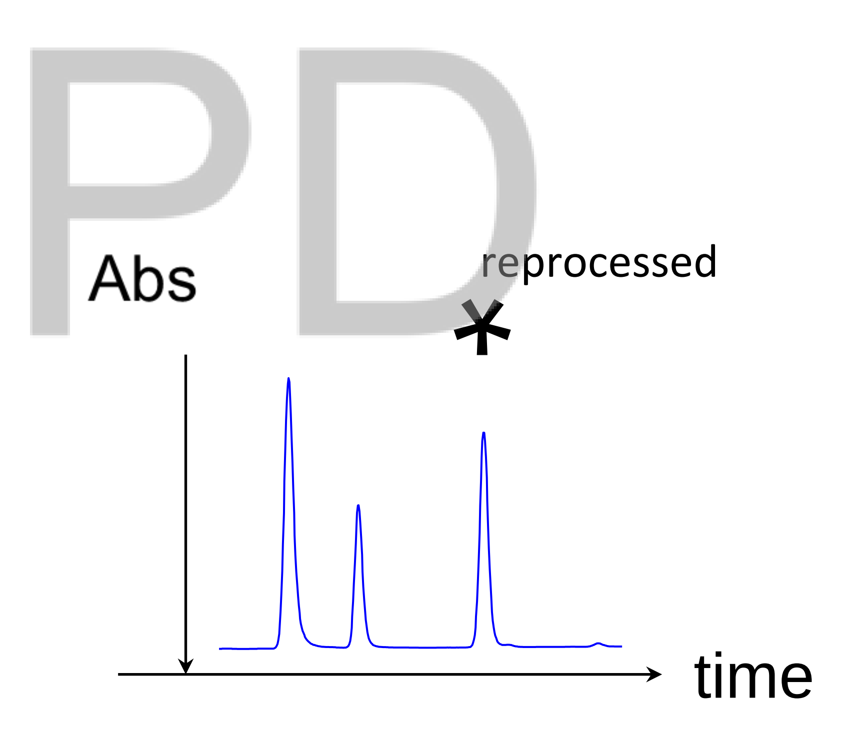


- Built-in checks for correct and secure entry and processing of data
- Additional check on accuracy for critical data entry
  - **By second operator**
  - By validated electronic means
- Criticality and potential consequences of erroneous or incorrectly entered data covered by **risk management**

Printouts



- Clear printed copies of electronically stored data
- For records supporting batch release
  - **Print-outs should indicate if any of the data has been changed since the original entry (audit trail)**



Audit Trails



- System audit trail should be considered for
  - Creation
  - Change
  - Deletion or records
- Reason for change
- Audi trail records should be convertible to a generally intelligible form
- Audit trail records should be **regularly reviewed**
  - **Include this as checklist item in batch record review**

Risk Based

Announce random audit trail review



Attachments

Validation Plan Template



Purpose of the Plan	
Product Description	
Validation Strategy	
Responsibilities (position)	
Supplier Assessment	
Risk assessment	
Testing Strategies and reporting	
DQ	
IQ	
OQ	
PQ	
Traceability matrix	
Procedures	
Approval	
Documents and control	





Req. ID	Requirement	Critical	Test Priority	Test ID
12.01	Data system should have computer generated, time-stamped audit trail to record the date and time of operator entries and actions that create, modify, or delete electronic record	high	high	T24
12.02	The system should allow optional entry of the reason for a change	high	high	T25

Installation Testing - Examples

System ID _____________ Date installed ____________

Test Objective: **Verify acceptable installation**

Installer Name _________________ Installer Signature _______________

Start: Log on as system administrator

Tester: I confirm that I have all tests executed as described

Name: ___________ Signature__________

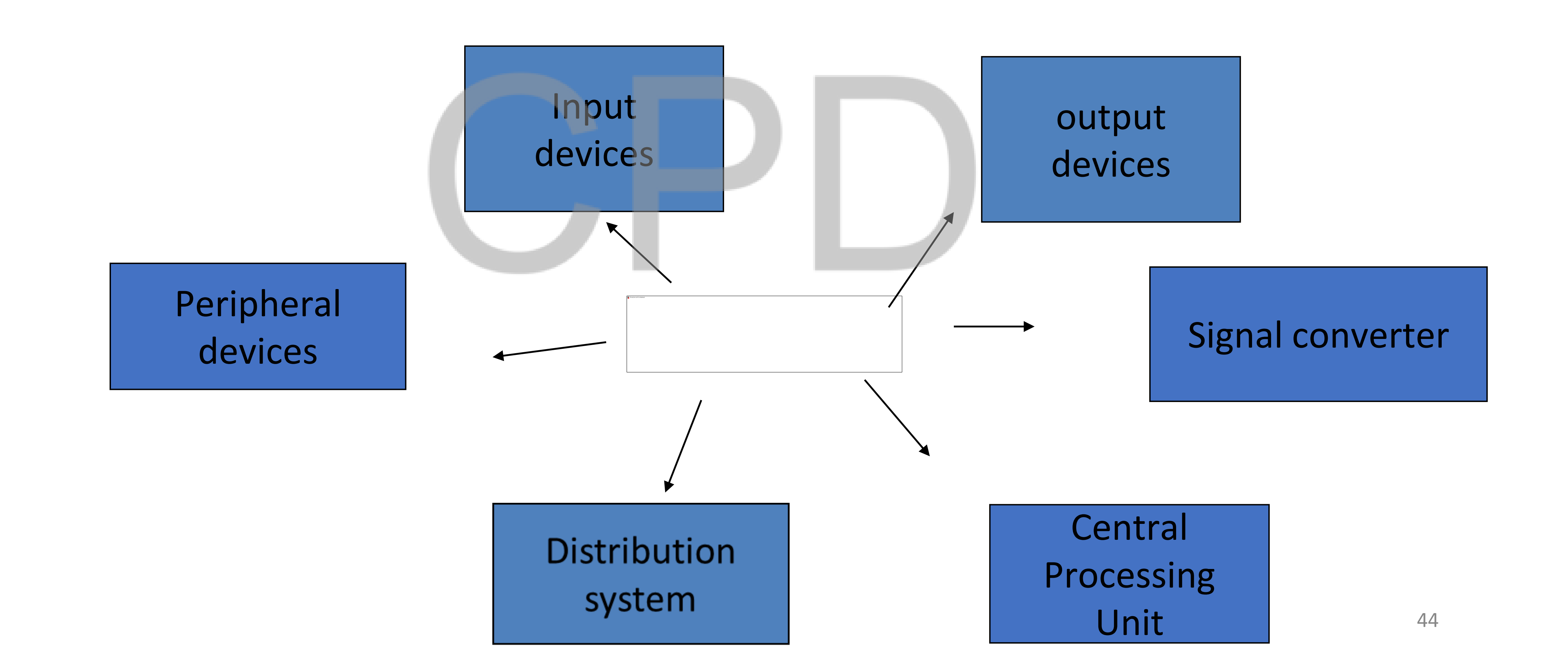
Date_________

Tests passed: yes no Comment:

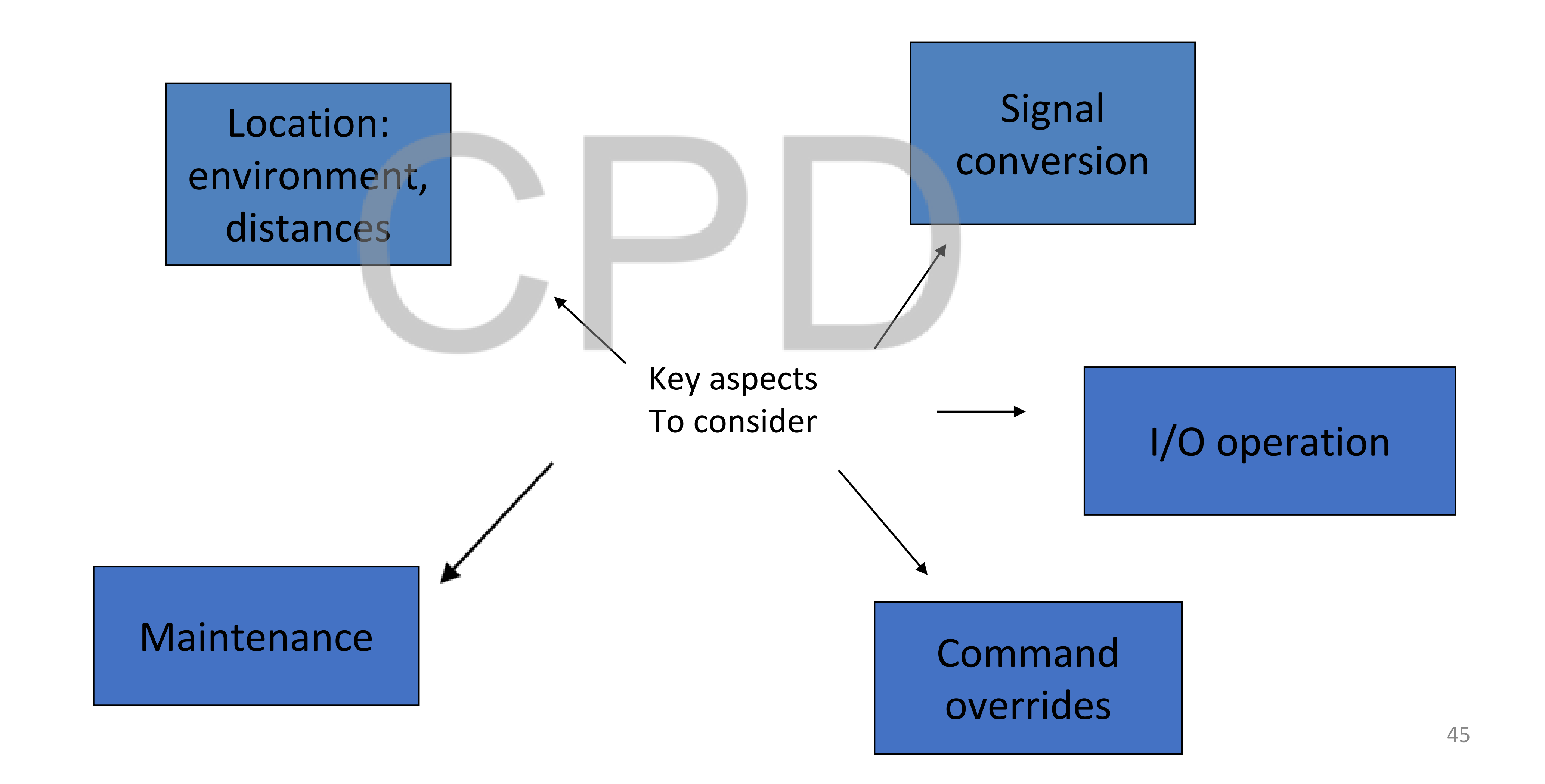
____

Test	Test Procedure	Pass	Fail
1	System log-on		
2	Load test method and instrument parameters		
3	Run well characterized test sample		
4	Compare with reference plot		
5	Document and sign results		
6	Access help file		

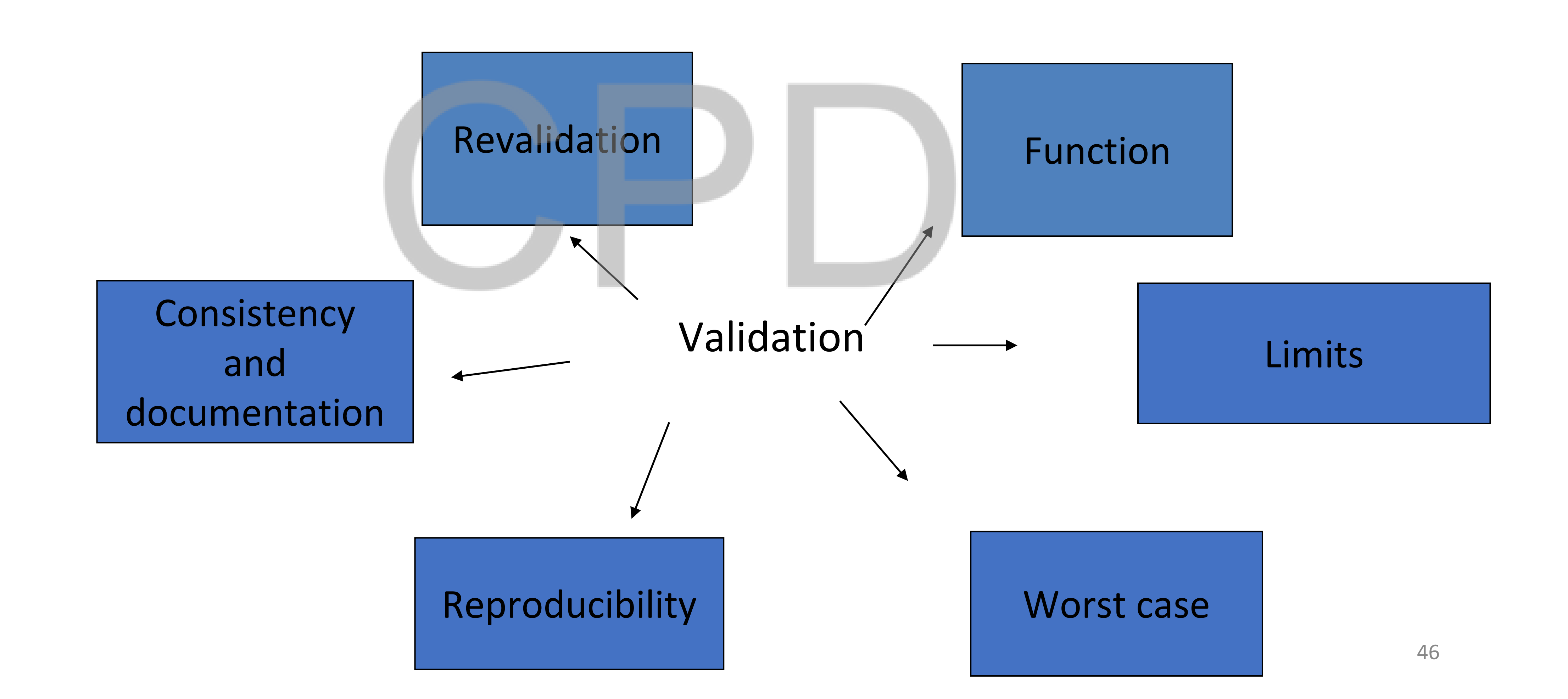
Summary: Validation requirements for Hardware (See table 1 in notes)



Summary: Validation requirements for Hardware (See table 1 in notes)

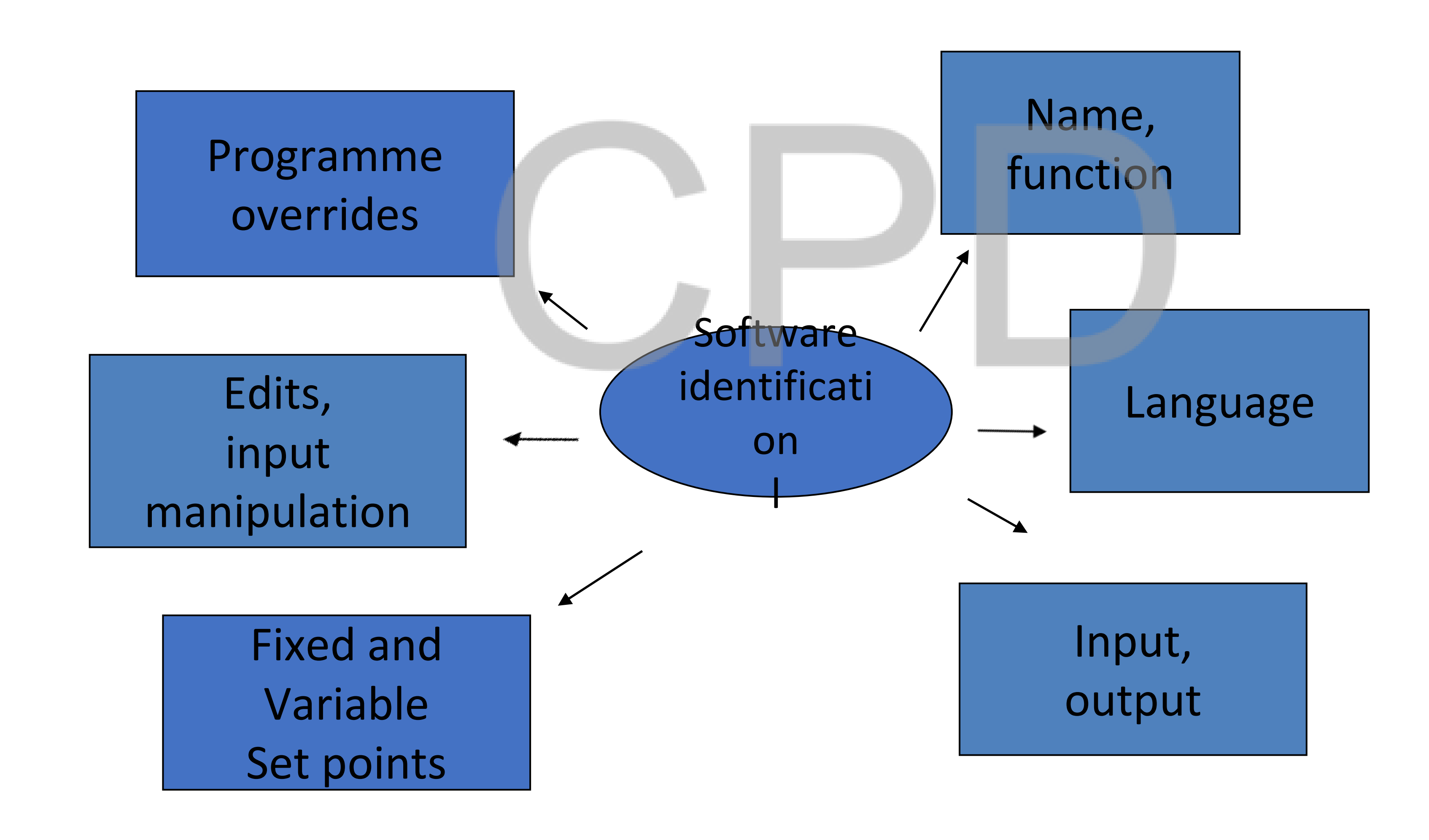


Summary: Validation requirements for Hardware (See table 1 in notes)



CPD

Summary: Validation requirements for Software (See table 2 in notes)



Summary: Validation requirements (See table 1 in notes)



Function

Documentatio
n

Validation

Worst case

Revalidation

Repeats

Computer System Validation:

Official Guidelines



- USP <1058> Analytical Instrument Qualification (Category C) (2008)
- PIC/S Good Practice Guide
  Using computers in GxP environments (2003)
- Japan MHLW : Guideline on Management of Computerized Systems for Marketing Authorization Holders and Manufacturers of Drugs and Quasi-drugs
- **GAMP 5 (2008)**
  A Risk based approach to Compliant GxP Computerized Systems
- **GAMP Good Practices Guide (2012)**
  A Risk based approach to GxP Compliant Laboratory Computerized Systems

PIC/S: Pharmaceutical Inspection Cooperation Scheme

GAMP® 5



A Risk Based Approach to Compliant GxP Computerized Systems

- Reference document for computer system validation
- Referenced in FDA and PIC/S Guides
- Uses V-lifecycle model, risk based approaches
- Defines four software categories (down from 5)
- Supplemented by Good Practices Guides for specific applications (lab systems, testing, data archiving)

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CPD



Thank you

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CPD
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PROFESSIONAL DEVELOPMENT
مركز التطوير المهني المستمر


EDA
EGYPTIAN DRUG AUTHORITY
هيئة الدواء المصرية
CPD





Process validation

Prepared by Dr. Amal Adel

Content

The Question of Process Validation



– Do I have confidence in my manufacturing process? Or, more specifically, what scientific evidence assures me that my process is capable of consistently delivering quality product?

– How do I demonstrate that my process works as intended?

– How do I know my process remains in control?





Process Validation ………..Why



- Why to validate a process?

- To reduce the production cost of Sorting and rework due to manufacturing of non-conforming products (products that doesn’t meet the specifications)

- To meet requirement of FDA and WHO ….and regulatory agencies.

- To prevent product recall from market.

Process Validation ………..Why



Learning progression

Good planning, expected path

- Comprehensive process design, scientific process understanding
- Sound, thorough process qualification. Confirms design
- Continued Verification, Process learning and improvement

Poor design, planning, process understanding

- Poor, minimal design
- PQ checklist exercise w/little understanding
- Unexplained variation, Product and process problems. Process not in control. **Major learning!** Potentially substandard product on market

Process Validation



US FDA

- Such validation is the collection and evaluation of data from the process design stage to commercial production, which establishes with scientific evidence that a process is capable of consistently delivering quality products

EMA

- Such validation comprises documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.



Process Validation lifecycle approach



- As per the lifecycle philosophy, process validation is not considered as a one-time activity, but rather an activity that spans the product lifecycle, linking ***process development, validation of the commercial manufacturing process, and its maintenance during routine commercial production.***



Process Validation lifecycle approach



- In the enhanced approach, manufacturing process performance is continuously monitored and evaluated.

- It is a scientific and risk-based real-time approach to verify and demonstrate that :

• a process operates within specified parameters
• consistently produces material that meets quality and process performance requirements.





Changes

Stage 1

Process Design

Evaluate / Confirm

Stage 2

Process Qualification

Design of Facilities & Qualification of Equipment and Utilities

Process Performance Qualification (PPQ)

Changes

Distribute

Stage 3

Continued Process Verification

Commercial Manufacturing

Stage 3a

Heightened sampling & testing until variability understood

Stage 3b

Routine monitoring program

Distribute

FDA Product Life Cycle — Process Validation



Process Validation Lifecycle Classification



The three-stage process validation lifecycle classification

Stage 1 – Process Design

Stage 2 – Process Qualification

Stage 3 – Continued Process Verification

Goals and typical activities of stage of process validation

ISPE



Stage of Process Validation	Definition	Goals	Typical Activities
Stage 1	Process Design	Define and design process	Build knowledge and understanding generated through development and scale-up activities and establishing a strategy for process control.
Stage 2	Process Qualification	Process design is evaluated to determine if the process **is capable** of **reproducible** commercial manufacturing	Design of a facility and qualification of utilities and equipment. A number of Process Performance Qualification (PPQ) batches to confirm the process design and demonstrate that the commercial manufacturing process performs as expected in the commercial manufacturing facility. Level of sampling may be higher than routine monitoring; the number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches.
Stage 3	Continued Process Verification (CPV)	Ongoing assurance that the process remains **in a state of control**	Ongoing programs to collect and analyze product and process data (monitoring plans) to assure the state of control of the process and verify impact of variability. Evaluating the performance of the process identifies potential issues and determines whether action must be taken to correct, anticipate, and prevent problems so that the process remains in control.





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Stage 1: Process Design
- Define the Knowledge Space
- Identify Critical Process Parameters
- Determine Control Strategy

Stage 2: Process Qualification
- Equipment / Utility / Facility Qualification
- Process Performance Qualification

Stage 3: Process Monitoring
- Monitoring of Critical Process Parameters as Part of APR and Other Monitoring Programs

Figure 1. The FDA Process Validation Model

Stage 1 – Process Design



- This stage cover all activities relating to product research and development, formulation, scale-up/ pilot batch studies and final transfer of technology to the manufacturing site.

- At the design stage itself, factors that may contribute to the quality of the product shall be carefully considered and this activity shall form the basis for the commercial manufacturing process. e.g.,

= selection of input material,

= components,

= product design, process design, etc………



Stage 1 – Process Design



- The physicochemical and biological properties of the drug substance that can influence the performance of the drug product and its manufacturability, or were specifically designed into the drug substance (e.g., solid state properties), should be identified



Stage 1 – Process Design



- Compatibility of excipients with other excipients, where relevant (for example, combination of preservatives in a dual-preservative system), should be established.

- The ability of excipients (e.g., antioxidants, penetration enhancers, dis-integrants , release controlling agents, etc.) to provide their intended functionality and to perform throughout the intended drug product shelf-life should also be demonstrated.

Stage 1 – Process Design



- Sources of knowledge available prior to (and that may be used during) Stage 1 of the Process Validation Lifecycle, include:

- Previous experience with similar processes (e.g., platform processes)
- Product and process understanding
- Analytical characterization
- Published literature
- Engineering studies/batches

Stage 1 – Process Design



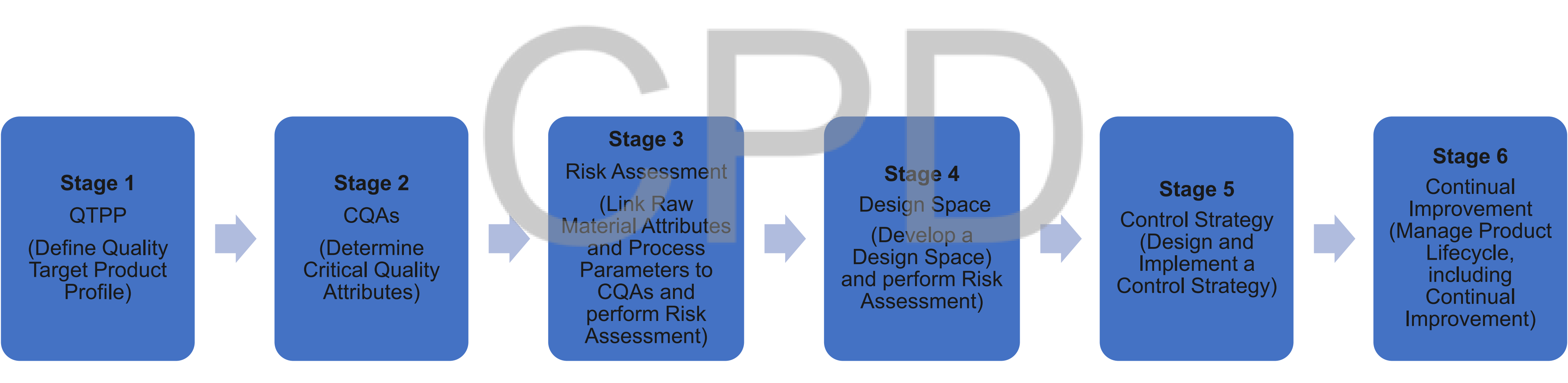
- In this stage, Product shall be developed as per QbD approach and the commercial manufacturing process shall be defined based on knowledge gained through development and scale up activities.

- Process control for each unit operation and overall process shall be established based on process knowledge and understanding.

- Strategies for process control shall be designed to reduce input variation, adjust for input variation during manufacturing (and so reduce its impact on the output).

QbD approach







What is Quality by Design (QbD)?



- A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. (ICH Q8 R2)





Systematic Approach	
Predefined objectives	- Define Quality Target Product Profile (QTPP) - Identify Critical Quality Attributes (CQA)
Product and process understanding	- Identify critical material attributes (CMA*) and critical process parameters (CPP) - Establish the functional relationships that link CMA/CPP to CQA
Process control	Develop appropriate Control Strategy, including justifications
Sound science	- Science-driven development (scientific literature,prior knowledge, DOEs etc.)
Quality risk management	- Risk-based development (ICH Q9)

Definitions



- Critical Process Parameter (CPP)

– A process parameter whose variability has an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality. (ICH Q8)

- Critical Material Attribute (CMA)

– A physical, chemical, biological or microbiological property or characteristic of an input material that should be within an appropriate limit, range, or distribution to ensure the desired quality of output material.

Definitions



- Critical Quality Attributes (CQA)

– A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (ICH Q8)

What is a Quality Target Product Profile (QTPP)?

- ICH Q8(R2) Definition:

A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy

- TPP: labeled use, safety and efficacy

- QTPP: quality characteristics to ensure safety and efficacy as promised in the label

Example QTPP



QTPP Elements	Target	Justification
Dosage form	Tablet	Pharmaceutical equivalence requirement: same dosage form
Dosage design	Immediate release tablet without a score or coating	Immediate release design needed to meet label claims
Route of administration	Oral	Pharmaceutical equivalence requirement: same route of administration
Dosage strength	20 mg	Pharmaceutical equivalence requirement: same strength
Pharmacokinetics	Immediate release enabling T_{max} in 2.5 hours or less; Bioequivalent to RLD	Bioequivalence requirement Needed to ensure rapid onset and efficacy
Stability	At least 24-month shelf-life at room temperature	Equivalent to or better than RLD shelf-life
Drug product quality attributes: Physical Attributes Identification Assay Content Uniformity Dissolution Degradation Products Residual Solvents Water Content Microbial Limits	Pharmaceutical equivalence requirement: Must meet the same compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality).	
Container closure system	Container closure system qualified as suitable for this drug product	Needed to achieve the target shelf-life and to ensure tablet integrity during shipping
Administration/Concurrence with labeling	Similar food effect as RLD	RLD labeling indicates that a high fat meal increases the AUC and C_{max} by 8-12%. The product can be taken without regard to food.
Alternative methods of administration	None	None are listed in the RLD label.

Example QTPP



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Example QTPP



Quality Attributes of the Drug Product		Target	Is this a CQA?	Justification
Physical Attributes	Appearance	Color and shape acceptable to the patient. No visual tablet defects observed	No	Color, shape and appearance are not directly linked to safety and efficacy. Therefore, they are not critical. The target is set to ensure patient acceptability.
	Odor	No unpleasant odor	No	In general, a noticeable odor is not directly linked to safety and efficacy, but odor can affect patient [illegible]. For this product, neither the drug substance nor the excipients [illegible] organic [illegible] will be used in the drug product manufacturing process. **Not a CQA**
	Size	Similar to RLD	No	For comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens, the target for tablet dimensions is set similar to the RLD.
	Score configuration	Unscored	No	The RLD is an unscored tablet; therefore, the generic tablet will be unscored. Score configuration is not critical for the acetriptan tablet.
	Friability	NMT 1.0% w/w	No	Friability is a routine test per compendial requirements for tablets. A target of NMT 1.0% w/w of mean weight loss assures a low impact on patient safety and efficacy and minimizes customer complaints.
Identification		Positive for acetriptan	Yes*	Though identification is critical for safety and efficacy, this CQA can be effectively controlled by the quality management system and will be monitored at drug product release. Formulation and process variables do not impact identity. Therefore, this CQA will not be discussed during formulation and process development.
Assay		100% w/w of label claim	Yes	Assay variability will affect safety and efficacy. Process variables may affect the assay of the drug product. Thus, assay will be evaluated throughout product and process development.
Content Uniformity (CU)		Conforms to USP <905> Uniformity of Dosage Units	Yes	Variability in content uniformity will affect safety and efficacy. Both formulation and process va[illegible]ity, so this CQA will be evaluated throughout product and process development. **CQA**
Dissolution		NLT 80% at 30 minutes in 900 mL of 0.1 N HCl [illegible] SLS	Yes	Failure to meet the dissolution specification can impact bioavailability. Both formulation and process [illegible] dissolution profile. This CQA [illegible]





1. Consider all DP quality attributes; physical attributes, identification, assay, content uniformity, dissolution and drug release, degradation products, residual solvents, moisture, microbial limits, etc.

2. Identify a CQA based on the severity of harm to a patient (safety and efficacy) resulting from failure to meet that quality attribute.

Quality Target Product Profile (QTPP)



Example: 500mg paracetamol tablet

Tablet Attribute*	Tablet QTPP
Dose	500mg Paracetamol tablet
Subjective properties	Appearance, uniform, no off taste or odour
Patient safety – chemical purity	Impurities and / or degradation products below ICH or to be qualified
Patient safety – biological purity	Acceptable level of non-pathogenic microorganisms, free from yeast or moulds or below the specified limit
Patient efficacy – particle size distribution (PSD)	PSD that does not impact bioperformance or pharmaceutical processing
Chemical and drug product stability:2 year shelf life, below 30°C	Degradation products below ICH or to be qualified and no changes in bioperformance over expiry period

*Only a few Paracetamol TPPs discussed here

From QTPP to CQAs



Example: 500mg paracetamol tablet

Paracetamol Product	Paracetamol QTPP*	Translation to CQA
Dose	500mg tablet	Identity, Assay, Uniformity of Dosage Units
Subjective properties	Appearance, uniform, no off taste or odour	All blisters filled, correct number of strips in pack, unit Integrity and other characteristics
Patient safety – chemical purity	Impurities and/or degradation products below ICH	Appearance and other characteristics Absence of defects
Patient safety – biological purity	Acceptable level of non-pathogenic microorganisms, free	Acceptable degradation product levels at release, appropriate manufacturing environment controls, input raw

Overall Process Assessment



Pre-blending
speed-
- load
time -
- size
Drying
-temp
- time
Blending
- load
-speed
-time
time-
-speed
force-
Granulation
Sizing
Compression



Overall Process Assessment



CQA	Dispensing	Blending	Granulation	Drying	Milling	Lubrication	Compression	Packing
Identity	Red	Green	Green	Green	Green	Green	Green	Green
Appearance	Green	Orange	Orange	Green	Green	Orange	Orange	Orange
Assay	Red	Red	Red	Green	Green	Green	Green	Green
Content Uniformity	Green	Orange	Orange	Green	Orange	Orange	Orange	Green
Purity	Orange	Orange	Orange	Green	Orange	Orange	Orange	Orange
Hardness	Green	Green	Orange	Orange	Green	Orange	Red	Green
Friability	Green	Green	Orange	Orange	Green	Orange	Orange	Green
Dissolution	Green	Green	Orange	Green	Orange	Red	Orange	Green

Red: Known or Potential impact to CQA
Orange: Potential impact to CQA
Green: No impact to CQA

Define the highest risk parameters and identify the CPPs

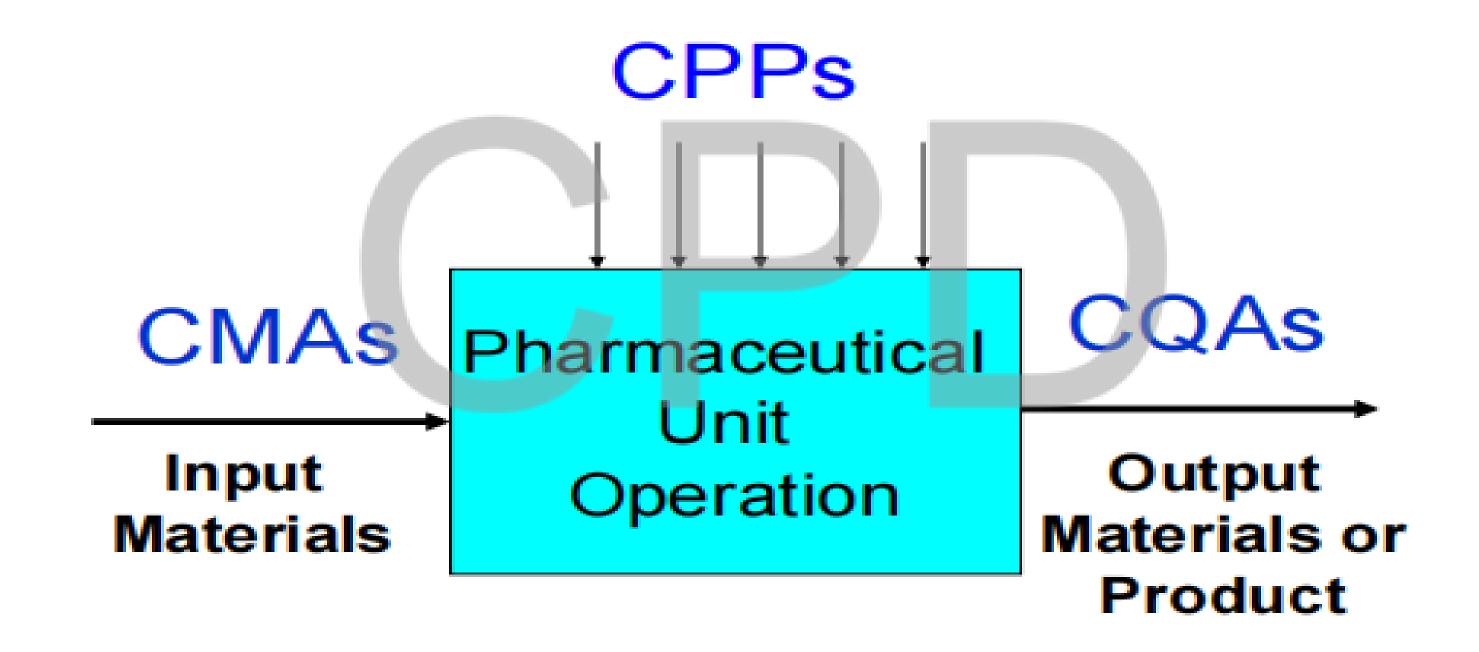


Overall Process Assessment



Relationship between CMAs, CPPs and CQAs





$$CQAs = f\,(CPP_1, CPP_2, CPP_3 \ldots CMA_1, CMA_2, CMA_3 \ldots)$$

Linking Patient - Product - Process



Patient

↕

Product

↕

Formulation /Process

Clinical Outcome
(Safety & Efficacy)

↕

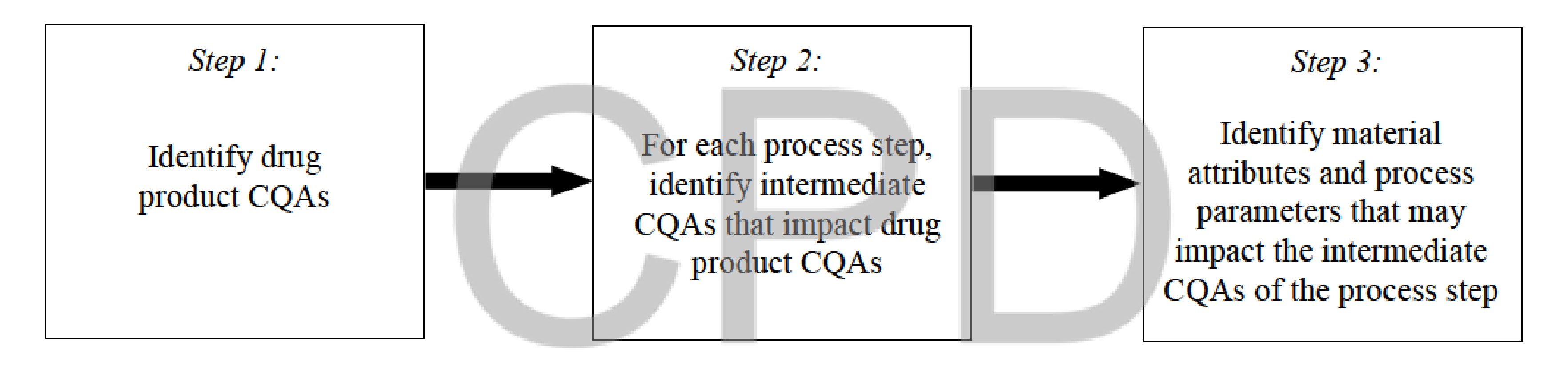
Critical Quality Attributes
(CQA)

↕

Critical Material Attributes
(CMA)
Critical Process Parameters
(CPP)

Example Approach to Identify Material Attributes and Process Parameters





Useful tools:

Risk assessment, prior knowledge, established science…..

Example Approach to Identify Material Attributes and Process Parameters



Step 1:	*Step 2:*	*Step 3:*
Identify drug product CQAs	For each process step, identify intermediate CQAs that impact drug product CQAs	Identify material attributes and process parameters that may impact the intermediate CQAs of the process step

Drug Product CQAs:	Intermediate CQAs:	Process Variables:
Content Uniformity	Blend Uniformity	1. Particle size distribution 2. Loading level 3. Number of revolutions

Example-1



- A fixed-dose combination IR tablet:

– API-1: ~80% of the tablet weight

– API-2: ~1% of the tablet weight

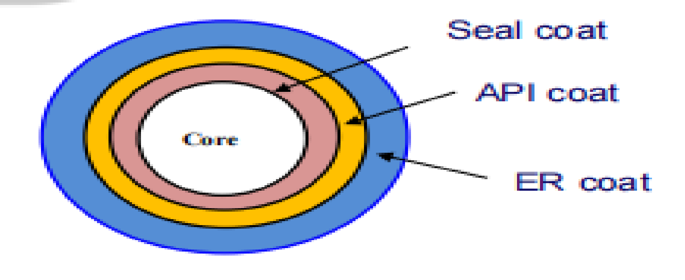
– Diluent (microcrystalline cellulose): ~ 14% of the tablet weight

– Other excipients: disintegrant, colorant, and lubricant

– Content Uniformity (CU) of API-2 is a high risk CQA

Example-2

- An Extended–Release (ER) Capsule
- API: 100 mg
  - highly soluble, excellent chemical stability, no polymorphism
- Manufacturing Process:
  - Seal-coated sugar sphere core
  - API coated pellets
  - ER polymer coated pellets
  - Encapsulation and packing
- Dissolution is a high risk CQA



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Identifying Potentially High Risk MAs or PPs



Input material attributes	Process parameters	Quality attributes
	Blending/mixing	
• Particle size	• Type and geometry of mixer	• Blend uniformity
• Particle size distribution	• Mixer load level	• Potency
• Fines/oversize	• Order of addition	• Particle size
• Particle shape	• Number of revolutions (time and speed)	• Particle size distribution
• Bulk/tapped/true density	• Agitating bar (on/off pattern)	• Bulk/tapped/true density
• Cohesive/adhesive properties	• Discharge method	• Moisture content
• Electrostatic properties	• Holding time	• Flow properties
• Moisture content	• Environment temperature and RH	• Cohesive/adhesive properties
		• Powder segregation
		• Electrostatic properties

- ➢ Special considerations for unique DS/DP properties

– e.g. RH can be potentially high risk for a hygroscopic formulation





“A planned set of controls, derived from current product and process understanding that ensures process performance and product quality.”

“The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control”.

Control Strategies and their rationale might include:

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Control Strategy Elements	Rationale
Raw Materials	Control of input variability
Test Specifications	Related to product safety/efficacy
In-Process Controls	Monitor the process
Performance Parameters	Cannot be controlled but are indicators
Set Points & Ranges	Known acceptable variability
Process Monitoring	Data collection for all Stages
Processing & Hold Times	Time limits impact product quality
Process Analytical Technology (PAT)	Real-time monitoring/release



Control strategy risk ranking



Control strategy factor	Source of potential variability and/or uncertainty	Relative risk ranking – Characteristics of ranking assignments		
		Low risk	Medium risk	High risk
Raw material specifications	• Different suppliers, different manufacturing processes • Material attributes test method • Different batches • Basis for material specification • Specification wider than experience	• Specifications of material attributes impacting product quality justified based on development data	• Limited justification of specifications of material attributes	• Specifications are not justified • Compendial or supplier limits accepted without further investigation
Equipment capability vs. process requirements	Capability of equipment to control operating parameters within acceptable ranges	Comparison of the parameter control ranges from equipment qualification with the process requirements indicates all parameters are well within equipment control capabilities and supported by qualification data	Comparison of control ranges from equipment qualification with process requirements indicates marginal capability to meet requirements for a limited number of process parameters	Comparison of parameter control ranges from equipment qualification with process requirements indicates a significant number of parameters are similar to equipment control capabilities
Experiences with process performance to date	• Variation observed • Scaling effects consistent with past performance	• Underlying cause(s) for variation is understood and addressed (or variation not observed during manufacture) • Impact of scale is well understood • Process has consistently performed as expected	• Variation is managed empirically, but underlying causes are not well understood • Some understanding of scaling issues. • Minor departures from expected results that were investigated and satisfactorily explained	• Variation has been observed, but has not been successfully managed • Impact of scale changes has not been explored. • Unexplained failure has been experienced
Monitoring capability and detectability	Ability of monitoring tools and methods to detect variation	Attributes measured in real time at sensitivity where performance variability is likely to be observed	Attributes measured offline (after batch completion) at a sensitivity where performance variability is likely to be observed	Attribute measurement sensitivity and/or accuracy are inadequate ~~to use~~ for controlling performance


Deliverables from stage 1 process validation



- Systematic approach, begin with the end in mind

- Identify CQAs based on patient's needs: **safety and efficacy**

- Use **science- and risk-based approach** to identify material attributes and/or process parameters that may impact CQAs

- development studies and focus on the **vital few potentially high risk material attributes and** process parameters

- Establish an appropriate **control strategy**

- Consider discussing **lifecycle management plans**



Process Validation Lifecycle Classification



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Figure 1. The FDA Process Validation Model

Stage 1: Process Design
- Define the Knowledge Space
- Identify Critical Process Parameters
- Determine Control Strategy

Stage 2: Process Qualification
- Equipment / Utility / Facility Qualification
- Process Performance Qualification

Stage 3: Process Monitoring
- Monitoring of Critical Process Parameters as Part of APR and Other Monitoring Programs



Process qualification (Stage 2)



- Process Qualification (PQ) during Stage 2 demonstrates that the process works as intended and yields reproducible commercial product. It should be completed before release of commercial product lots, and covers the following elements:

- Design and qualification of the facility, equipment, and utilities (this should be completed prior to qualification of the process).

- Process Performance Qualification (PPQ), which demonstrates control of variability and the ability to produce product that meets predetermined quality attributes

Process qualification (Stage 2)

1-system design and qualification



- Facilities, Personnel, equipment, utilities, and instruments (collectively referred to as systems) used in the manufacturing process should be suitable and capable for their intended process use, and their performance during the operation should be reliable.

- The review and qualification of these systems should be performed according to a pre-defined project plan.

- The stages of qualification of equipment may include design, installation, operation and performance of equipment .

- Qualification studies should be completed, reviewed , and approved, with all deviations addressed, prior to the start of PPQ studies.

- Systems that affect product quality should be qualified to reduce a process variability.

Process qualification (Stage 2)
2-Process performance qualification



- Traditionally, three batches have been considered the normal and acceptable number for process validation; however, the number of batches should be justified and based on a risk assessment that includes, for example, variability of results from the process design stage, variability of materials, product history, where the product is being transferred from and where it will be produced.

- Manufacturers should define the stage at which the process is considered to be validated and the basis on which that decision was made.

- The decision should include a justification for the number of batches used based on the complexity and expected variability of the process and critical quality attributes (CQAs)

Process qualification (Stage 2)
2-Process performance qualification



- Successful completion of process performance qualification stage of the life-cycle is required for commercial distribution.
- A risk assessment should be performed for the change from scale-up to commercial batch size.
- Process qualification should confirm that scale-up in batch size did not adversely affect the characteristics of the product and that a process that operates within the predefined specified parameters consistently produces a product that meets all its CQAs and control strategy requirements.
- The process should be verified on commercial-scale batches prior to marketing of the product.

Process qualification (Stage 2)
2-Process performance qualification



- Validation should be done in accordance with process validation protocols.
- A written protocol is essential for this stage of process validation.
- The protocol should include or reference at least the following elements:

■ the manufacturing conditions, including operating parameters, processing limits and component (raw material)inputs;

■ the data to be collected and when and how they will be evaluated;

■ the type of testing or monitoring to be performed (in-process, release, characterization) and acceptance criteria for each significant processing step;

Process qualification (Stage 2)
2-Process performance qualification



■ the scientifically justified sampling plan, including sampling points, number of samples and the frequency of sampling for each unit operation and attribute;

■ the number of batches for which additional monitoring is proposed;

■ status of the validation of analytical methods used in measuring the process, in-process materials and the product;

■ a description of the statistical models or tools used;

Process qualification (Stage 2)
2-Process performance qualification



■ review and approval of the protocol by appropriate departments and the quality unit;

■ a description of the process;

■ details of the equipment and/or facilities to be used (including measuring or recording equipment) together with its calibration status;

■ the variables to be monitored, with appropriate justification;

■ the samples to be taken

Process qualification (Stage 2)
2-Process performance qualification



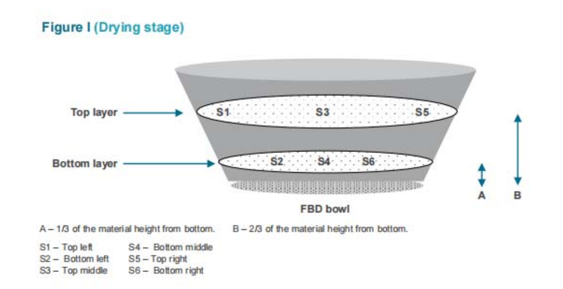
- the product performance characteristics or attributes to be monitored, together with the test methods;
- the acceptable limits;
- personnel responsibilities;
- details of methods for recording and evaluating results, including statistical analysis.

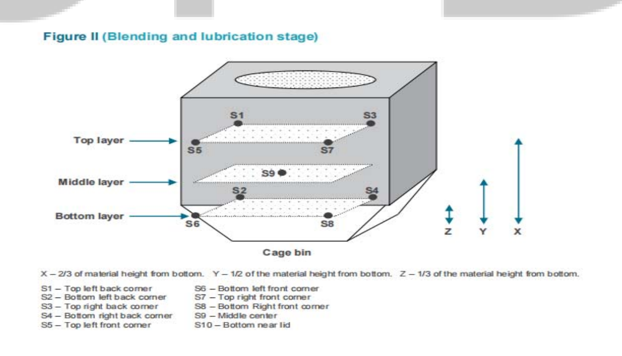
Data should be collected and reviewed against predetermined acceptance criteria and fully documented in process validation reports.

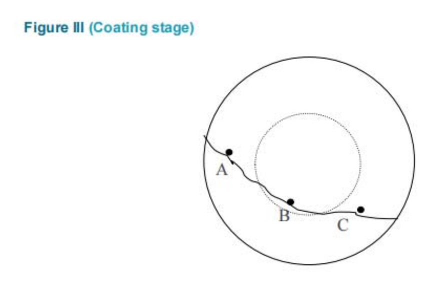
Process qualification (Stage 2)
2-Process performance qualification



- In most cases, PPQ will have a higher level of sampling, additional testing, and greater scrutiny of process performance than would be typical of routine commercial production.
- the samples to be taken “who”, “where”, “when”, “how”, “how many” and “how much” (sample size)







Sampling plan for PPQ of drug products



Manufacturing stage[1]	Process variables	Sampling stages	Tests to be performed	Approx. Sample Size *(Wherever applicable, pictorial representation of the sampling locations should be given in the PPQ Protocol)*	Acceptance criteria for quality attributes
Cream/ointment (after bulk preparation)	Temperature at which final mixing is done (°C)	Time intervals to be fixed in PPQ Protocol	Bulk uniformity/ Homogeneity of drug	• Number of locations should be fixed based on mixing vessel design • Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification
	Stirring speed		Viscosity		
	Stirring time		pH		
Cream/ointment (filling operation)	Machine speed	Time intervals to be fixed in PPQ Protocol (Guidance: Start, middle and end of a filling cycle)	Average fill weight/weight variation	• Each filling station should be considered for sampling at fixed duration • Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification
			Uniformity of content		
			Leak test		
Liquid orals/ suspension (after bulk preparation)	Stirring time	Time intervals to be fixed in PPQ Protocol	Bulk uniformity/ Homogeneity of drug	• Number of locations should be fixed based on mixing vessel design • Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification
	Stirring speed		pH		
			Weight per ml.		

Sampling plan for PPQ of drug products



Manufacturing stage[1]	Process variables	Sampling stages	Tests to be performed	Approx. Sample Size *(Wherever applicable, pictorial representation of the sampling locations should be given in the PPQ Protocol)*	Acceptance criteria for quality attributes
Liquid orals/ suspension (filling operation)	Machine speed Machine speed	Time intervals to be fixed in PPQ Protocol	Average fill volume/ Uniformity of volume Uniformity of content Leak test	▪ Each filling station should be considered for sampling at fixed duration ▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification
Dry syrup (filling and sealing)	Hopper level Machine speed	Time intervals to be fixed in PPQ Protocol (Guidance: start, middle and end of Filling/Sealing Process)	Average fill weight/uniformity of weight (as applicable) Reconstitution time Uniformity of content	▪ Each filling station should be considered for sampling at fixed duration ▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification
Primary packaging (bottles for dry syrup, suspension, liquid orals, tablets, capsules)	Power to induction sealer	Time intervals to be fixed in PPQ Protocol (Guidance: start, middle and end of Packaging)	Leak test Assay (in case of heat-sensitive product)	▪ Each filling station should be considered for sampling at fixed duration ▪ Sample size should be decided based on type of product and should be specified in PPQ Protocol	As per approved specification

Note: In case of direct blending in solid dosage forms, stratified sampling is preferable.
1 Samples for hold-time study shall also be withdrawn at appropriate stages, as per requirement.

Process qualification (Stage 2)
2-Process performance qualification



- A report should reflect the validation protocol.
- A dual protocol report can be used; however, such reports must be designed to ensure clarity and sufficient space for recording of results.
- The outcome should confirm that the acceptance criteria have been met.

Process qualification (Stage 2)
2-Process performance qualification



- Any deviations (including abandoned studies) should be explained and justified.
- The planned commercial production and control records, which contain the operational limits and overall strategy for process control, should be carried forward to the next phase for confirmation.
- Retrospective validation no longer acceptable.
- Concurrent validation only acceptable where there is a strong benefit-risk ratio for the patient.

Process qualification (Stage 2)
2-Process performance qualification



- granulations: moisture (limits expressed as a range), blend uniformity (e.g. low dose tablets), bulk and tapped densities, particle size distribution;
- solid oral products: average weight, weight variation, hardness, thickness, friability, and disintegration checked periodically throughout compression, weight gain during coating;
- semi-solids: viscosity, homogeneity, pH;
- transdermal dosage forms: assay of API–adhesive mixture

Process qualification (Stage 2)
2-Process performance qualification



- metered dose inhalers: fill weight/volume, leak testing, valve delivery;
- dry powder inhalers: assay of API–excipient blend, moisture, weight variation of individually contained doses such as capsules or blisters;
- liquids: pH, specific gravity, clarity of solutions;
- parenteral: appearance, clarity, fill volume/weight, pH, filter integrity tests, particulate matter, leak testing of ampoules, pre-filtration and/ or pre-sterilization bioburden testing.



Process qualification (Stage 2)

PPQ protocol & Report

Process qualification (Stage 2)

PPQ protocol



- PPQ protocols are documented plans for executing the PPQ studies.
- Protocols are reviewed and approved by cross-functional groups that include the quality unit.
- Protocols must be approved prior to commencement of PPQ activities.

Process qualification (Stage 2)

PPQ protocol



- PPQ protocols typically contain the sections described below.

Introduction

- The introduction should include a description of the process and/or specific unit operations under qualification, including the intended purpose of the operations in the context of the overall manufacturing process.
- The introduction should provide an overview of the study or studies, and other important background information.

Purpose and scope

- This section describes the objective of the study and provides an overview of the study strategy, i.e., how it will be performed, how data will be analyzed, and the expected outcome.
- Justifications or cross-referencing to documents that contain justifications, such as the process validation master plan, should be included

Process qualification (Stage 2)

PPQ protocol



References

References to relevant documents related to the study should be included in the protocol:

- Development and/or process characterization reports that provide supporting data for operational parameter and attribute ranges.
- Process design report.
- Process validation master plan.
- Commercial manufacturing batch records.
- Related qualification documents (facilities, utilities, equipment, other PPQ studies, etc.).
- Analytical methods.
- Specification documents.
- Approved batch records.

Process qualification (Stage 2)

PPQ protocol



Equipment and materials

- A list of equipment, instrumentation, and materials necessary to perform the study should be included.
- References to qualification of utilities and equipment should be provided as appropriate.

Responsibilities

- This section shall include a designation of various functional groups and their responsibilities as they relate to execution of the study, and verification that appropriate training has been conducted for all contributors.

Process qualification (Stage 2)

PPQ protocol



Description of unit operation/process

- The objective of PPQ is to provide confidence that all elements of unit operation/process are under the appropriate degree of control.

- A comprehensive discussion of the control strategy similar to the level of detail provided in the commercial manufacturing control strategy is appropriate to demonstrate that all process elements have been considered.

- Although all elements are described, only a subset of the process variables will comprise PPQ acceptance criteria.

Process qualification (Stage 2)

PPQ protocol



Methodology

- This describes the step-by-step procedure needed to perform the study.
- This section clearly identifies the critical and key process parameters under qualification and the methods by which the operation will be monitored and recorded.
- A brief explanation of the relevance of these parameters and their potential relationship to process performance and quality attributes is useful to further describe the PPQ strategy.
- Documents containing the detailed rationale for critical and key parameter designations should be referenced.
- A discussion of the number of batches planned should be included, and the rationale should be stated.

Process qualification (Stage 2)

PPQ protocol



Data collection

- Roles and responsibilities for various functional groups as they relate to collection and analysis of PPQ data and documentation should be included.

- The list of process data to be collected and how it will be analyzed should be stated.

Process qualification (Stage 2)

PPQ protocol



Sampling plan

- This is the description of a defined prospective sampling plan and its operating characteristic curve with details on the number of samples, frequency of sampling, and sampling points supported by statistical justification, as applicable.

- The typical contents of such a plan should include:
  - Sampling points.
  - Number of samples and statistical basis for sampling, as appropriate.
  - Sample volume.
  - Non-routine sampling for extended characterization.
  - Sample storage requirements.
  - Analytical testing for each sample.

Process qualification (Stage 2)

PPQ protocol



Analytical testing

- The overall validation package includes the methods used for all analytical testing performed, from assessment of raw materials to extended characterization of the drug product.

- A listing of all analytical methods used in each protocol and the validation or qualification status of each (and references to source documents) should be included.

- Analytical method validation should also be included as part of the process validation master plan.

Process qualification (Stage 2)

PPQ protocol



Deviations

- All potential deviations cannot be anticipated regardless of the level of characterization and knowledge.

- A general framework for defining the boundaries of qualification is appropriate and, as an example, should describe the following:

- Out-of-specification or out-of-limits test results.
- Failure of a CPP to remain within normal operating range; a CPP is designated as such due to the potential impact on a corresponding CQA. Failure to control may indicate overconfidence in an immature control strategy. This would be grounds for protocol failure.
- Missed samples or samples held under incorrect storage conditions.
- How individual batches or lots failing to meet validation acceptance criteria will impact the study.

Process qualification (Stage 2)

PPQ protocol



Acceptance criteria for PPQ

- The objective of PPQ is to demonstrate that the commercial manufacturing process is in a state of control, and the elements of the process control strategy provide confidence that a state of control will be maintained.

- The protocol should clearly document the acceptance criteria to be met in order for the PPQ to be considered successful.

- Acceptance criteria may be shown in tabular format in the protocol

Process qualification (Stage 2)

PPQ report



A report should be prepared for each study and should typically include the following sections:

Introduction

This section should include a concise description and outline of the unit operations or group of unit operations that have been qualified. It should summarize the overall results of the study, providing back ground information and explanations as necessary.

Methods and materials

This provides a clear and concise summary of how the study was performed. It should identify how the objectives of the study were accomplished using both methodology and references to appropriate procedures and protocol requirements.

Process qualification (Stage 2)

PPQ report



Deviations

- A summary of the deviations and corresponding root causes, as well as a discussion of the potential impact to the PPQ , should be included.
- Corrective actions resulting from deviations should be discussed.
- Their impact on the process, the PPQ , and on the affected batches should be provided.

Protocol excursions

- Protocol excursions and unexpected results should be included and fully described in the report.
- A reference to the root cause analysis should be provided if documented separately from the PPQ

report .

- Any corrective actions and their impact on PPQ should be outlined in the report.

Process qualification (Stage 2)

PPQ report



Discussion: PPQ results

- This section should restate the key and critical process parameters and give the actual range of values occurring during the PPQ.
- It should include how the data were collected as well as references for analytical methods used.
- Data summarized and compared with pre-defined acceptance criteria should be presented in tabular or graphical format whenever possible, and data used from Stage 1 studies should be clearly identified.

Process qualification (Stage 2)

PPQ report

Discussion: PPQ results cont.

- The discussion should provide support for any study conclusions.
- The impact of ranges and deviations should be discussed if they affect the study results.
- Risk assessment and any follow-up conclusions, including corrective actions, should be stated.
- Findings associated with batches or lots that fail to meet the acceptance criteria in the protocol should be referenced in the final PPQ package; likewise, with any corrective measures taken in response to the cause of failure.

Process qualification (Stage 2)

PPQ report



Conclusions

- Conclusions as to whether data demonstrate that the process is in a state of control should be provided.
- Pass or fail results should be stated for each acceptance criteria and corresponding results.
- When a unit operation approach is used, PPQ reports should be prepared for each unit operation study.
- A summary executive report that unifies all the study results to support the overall process PPQ should be written.



Process Validation Lifecycle Classification



2011
FDA Process
Validation
Guidance

Figure 1. The FDA Process Validation Model

Stage 1: Process Design
- Define the Knowledge Space
- Identify Critical Process Parameters
- Determine Control Strategy

Stage 2: Process Qualification
- Equipment / Utility / Facility Qualification
- Process Performance Qualification

Stage 3: Process Monitoring
- Monitoring of Critical Process Parameters as Part of APR and Other Monitoring Programs

Continued process verification

(Stage 3)

- Manufacturers should monitor the product quality of commercial batches after completion of process design and process qualification.

- This will provide evidence that a state of control is maintained throughout the product life-cycle.



Continued process verification

(Stage 3)

- The scope and extent of process verification will be influenced by a number of factors, including:

■ *prior development and knowledge of the manufacturing of similar products and/or processes;*

■ *the extent of process understanding gained from development studies and commercial manufacturing experience;*

■ *the complexity of the product and/or manufacturing process;*

■ *the level of process automation and analytical technologies used;*

■ *for legacy products, with reference to the product life-cycle process, robustness and manufacturing history since the*

point of commercialization, as appropriate.

Continued process verification

(Stage 3)

- Manufacturers should describe the appropriateness and feasibility of the verification strategy (in the protocol), including the process parameters and material attributes that will be monitored, as well as the validated analytical methods that will be employed.

- Manufacturers should define:

■ *the type of testing or monitoring to be performed;*
■ *the acceptance criteria to be applied;*
■ *how the data will be evaluated and the actions to be taken.*



Continued process verification

(Stage 3)

- Any statistical models or tools used should be described.

- If continuous processing is employed, the stage at which the commercial process is considered to be validated should be stated, based on the complexity of the process, expected variability and manufacturing experience of the company.

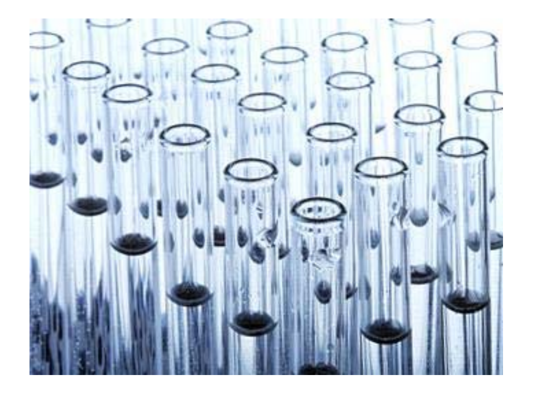
- Periods of enhanced sampling and monitoring may help to increase process understanding as part of continuous improvement.

Continued process verification

(Stage 3)

- Information on process trends, such as the quality of incoming materials or components, in process and finished product results and non-conformances, should be collected and assessed to verify the validity of the original process validation or to identify changes to the control strategy required.

- The scope of continued process verification should be reviewed periodically, and modified if appropriate, throughout the product life-cycle.





Change management



- Manufacturers should follow change-control procedures when changes are planned to existing systems or processes.
- The change-control procedure and records should ensure that all aspects are thoroughly documented and approved, including regulatory approval where appropriate (variation).
- Sufficient data should be generated to demonstrate that the revised process will result in a product of the desired quality, consistent with approved specifications.
- Validation should be considered when changes to production and/or control procedures are planned.





- Based on risk assessment, changes that may require revalidation could include (but are not limited to):

■ changes in the master formula, methods, starting material manufacturer, starting material manufacturing process, excipient manufacturer, excipient manufacturing process;

■ changes in the equipment or instruments(e.g. addition of automatic detection systems);

■ changes associated with equipment calibrations and the preventive maintenance carried out, which may impact the process;

■ production area and support system changes(e.g.re-arrangement of areas or a new water-treatment method);

Change management



■ changes in the manufacturing process (e.g. mixing times, drying temperatures);

■ transfer of processes to another site;

■ unexpected changes (e.g. those observed during self-inspection or during routine analysis of process trend data);

Change management

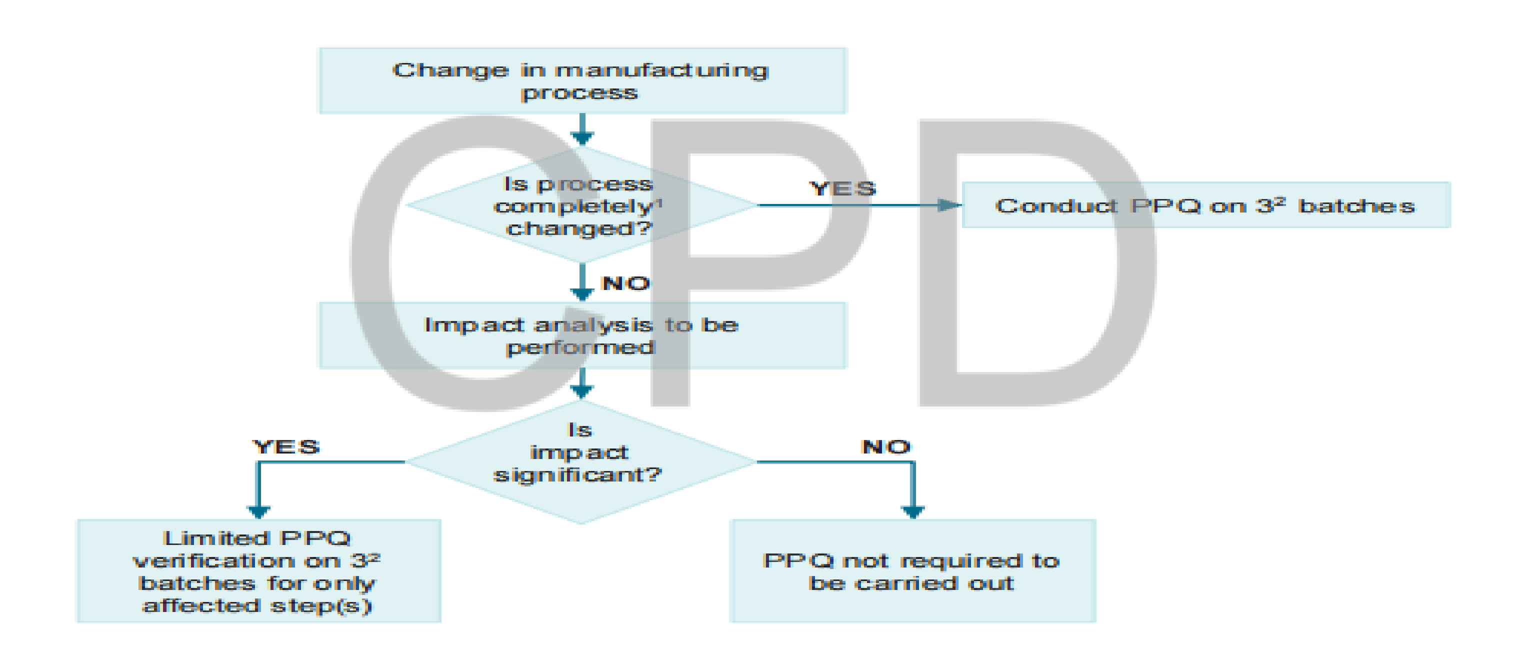


■ changes to standard operating procedures;

■ changes to cleaning and hygiene programs.

Depending upon the nature of the change being proposed, the process should consider whether existing approved specifications will be adequate to control the product subsequent to implementation of the change.

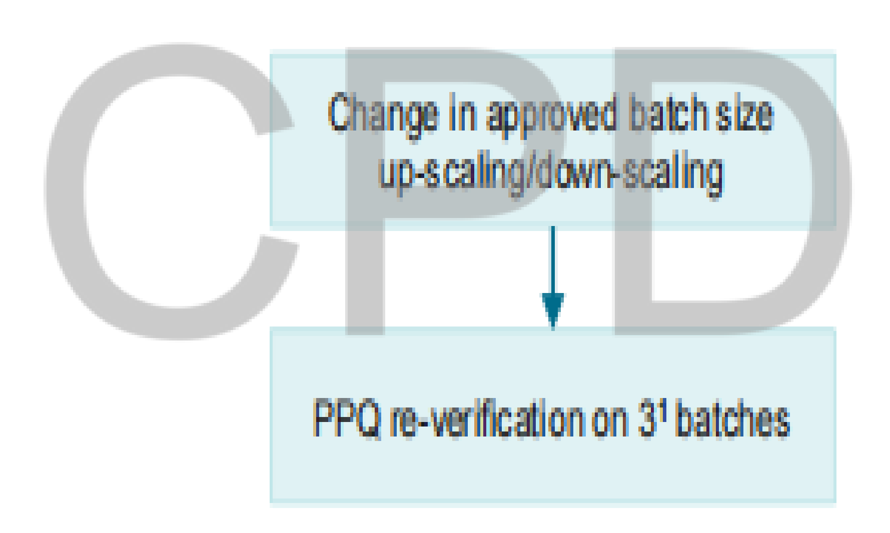
PPQ for change in approved manufacturing process



This is for guidance purpose only, may change based on regulatory requirements, product specific requirements, change control evaluation, etc.

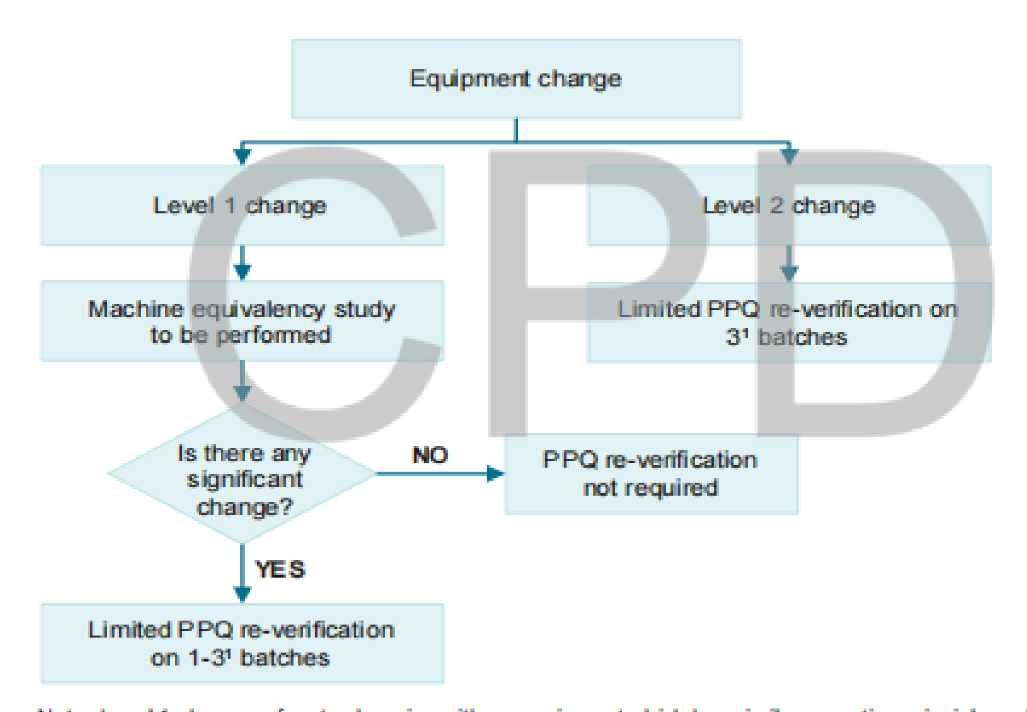
PPQ for change in batch size





This is for guidance purpose only, may change based on regulatory requirements, product specific requirements, change control evaluation, etc.

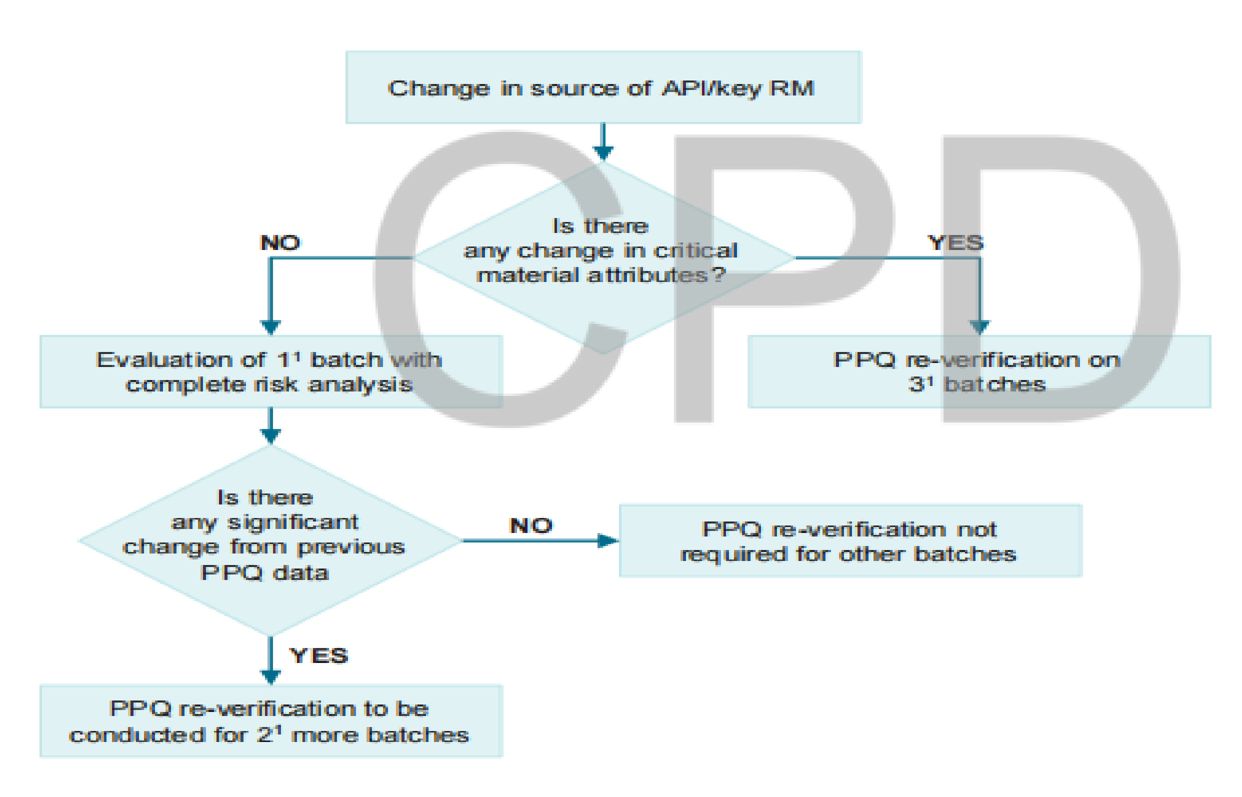
PPQ for change in equipment



This is for guidance purpose only, may change based on regulatory requirements, product specific requirements, change control evaluation, etc.

PPQ for change in source of API/key RM

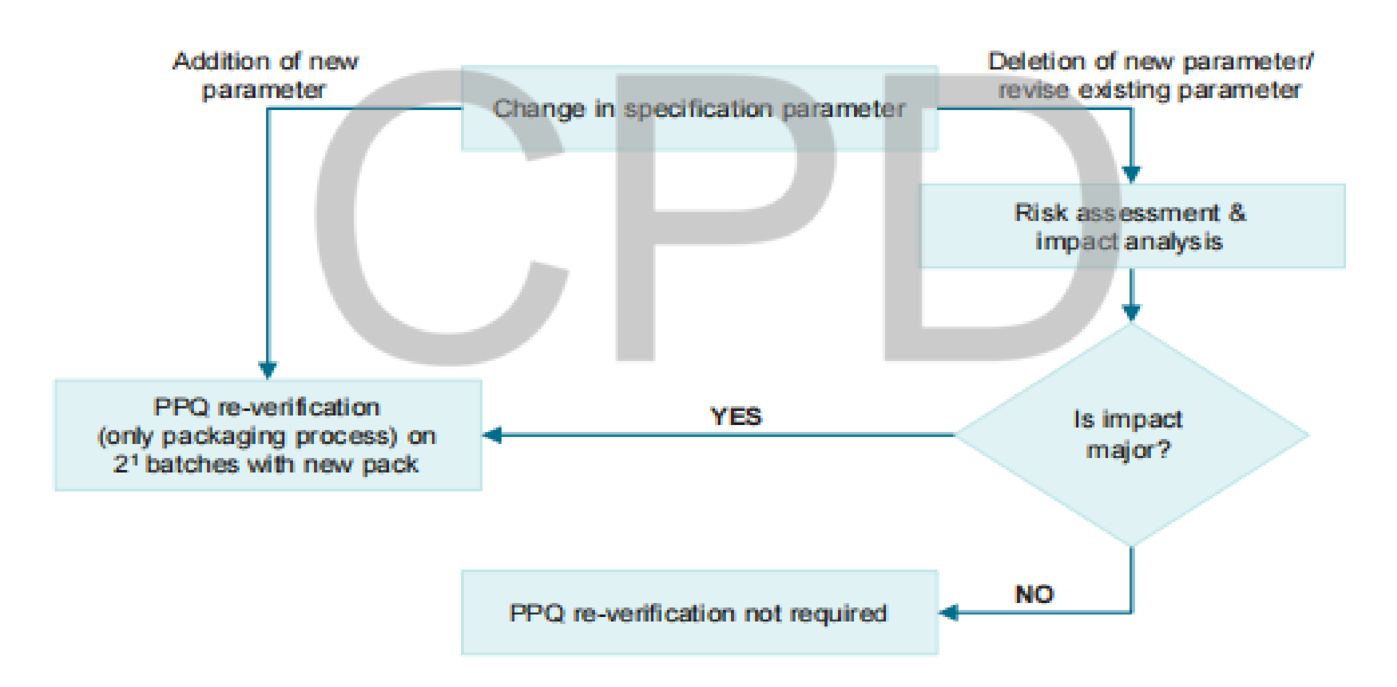




This is for guidance purpose only, may change based on regulatory requirements, product specific requirements, change control evaluation, etc.

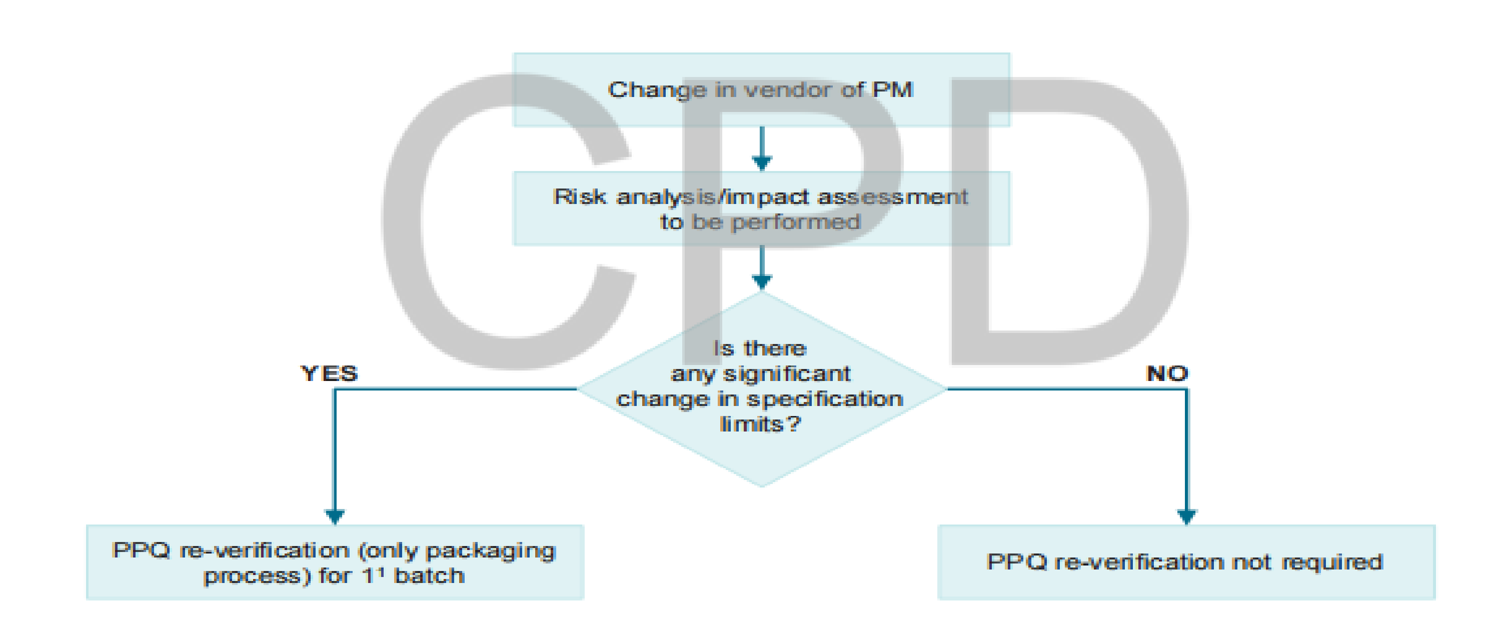
PPQ for change in specification of primary pack of finished product





This is for guidance purpose only, may change based on regulatory requirements, product specific requirements, change control evaluation, etc.

PPQ for change in vendor of PM



This is for guidance purpose only, may change based on regulatory requirements, product specific requirements, change control evaluation, etc.



Process Capability Formulas



C_{pk}	The lower of the C_{pu} and the C_{pl}
C_{pl}	$C_{pl} = \frac{(\overline{\overline{X}} - LSL)}{3s}$
C_{pu}	$C_{pu} = \frac{(USL - \overline{\overline{X}})}{3s}$
C_{pm}	$C_{pm} = \frac{USL - LSL}{6\sqrt{(\overline{X} - T)^2 + s^2}}$
Estimated Sample Standard Deviation	$s \approx \frac{\overline{R}}{d_2}$
Grand Average	$\overline{\overline{X}} = \frac{\sum \overline{X}}{k}$
Mean	$\overline{X} = \frac{\sum X}{n}$
Process Capability Index	$C_p = \frac{USL - LSL}{6s}$
Process Capability Ratio	$C_r = \frac{6s}{USL - LSL} \times 100\%$
Range	R = highest point - lowest point
Sample Standard Deviation	$s = \sqrt{\frac{\sum (X - \overline{X})^2}{n - 1}}$
P_{pk}	The lower of the P_{pu} and the P_{pl}
P_{pl}	$P_{pl} = \frac{\overline{X} - LSL}{3s}$
P_{pu}	$P_{pu} = \frac{USL - \overline{X}}{3s}$
Process Performance Index	$P_p = \frac{USL - LSL}{6s}$



Process Capability Formulas



Short -Term Capability Indices

$$C_p = \left(\frac{USL - LSL}{6s}\right)$$

$$C_{pk} = min(C_{pk(USL)}, C_{pk(LSL)})$$

$$C_{pk(USL)} = \left(\frac{USL - \bar{X}}{3s}\right)$$

$$C_{pk(LSL)} = \left(\frac{\bar{X} - LSL}{3s}\right)$$

Long -Term Capability Indices

$$P_p = \left(\frac{USL - LSL}{6\sigma}\right)$$

$$P_{pk} = min(P_{pk(USL)}, P_{pk(LSL)})$$

$$P_{pk(USL)} = \left(\frac{USL - \mu}{3\sigma}\right)$$

$$P_{pk(LSL)} = \left(\frac{\mu - LSL}{3\sigma}\right)$$

T

LSL - 3s

+ 3s USL

Process Width

Design Width





- The life-cycle approach links product and process development, validation of the commercial manufacturing process and maintaining the process in a state of control during routine commercial production.

- The use of process analytical technology (PAT), which may include in-line, online and/or at-line controls and monitoring, is recommended to ensure that a process is in a state of control during manufacture.

Conclusion



- The validation should be carried out in accordance with GMP and data should be held at the manufacturing location whenever possible and should be available for inspection.

A: Process validation lifecycle



Process validation

Stage 1
Process design

- Establish-ing A strategy for process controls
- Building & capturing process knowledge and under-standing

Stage 2
Process Qualification (PQ)

- Design and qualification of facility, equipment and utilities
- Process Performance Qualification (PPQ)
  - Option 1 – prospec-tive approach
  - Option 2 – con-current approach

OK → Commercial distribution of batches

Not OK → One or more of the following steps may be taken; but not limited to:

- Re-testing for confirmation
- Change in operating parameters, process steps
- Changing process equipment/procedure for use
- Suspension of PPQ until technical evaluation and/or development has been done
- Change the sampling regime
- Review of historical data & drawing of hints for the failure
- Change PPQ acceptance criteria
- Change analytical procedure

As an output of change assessment

In case of failures in commercial mfg.

Repeat PPQ – complete/limited steps

As an output of CPV

Stage 3
Continuous Process Verification (CPV)

- Post PPQ batches' evaluation
- APR/PQR
- Timely assessment of CC, deviations, OOS, OOT, Complaints, etc.
- Maintaining quality of incoming materials/ components
- In-process & finished product testing program
- Facility/equipment maintenance



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Thank you


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HVAC SYSTEMS, QUALIFICATION AND INSPECTIONS

Presented by:
Dr. Mohamed Salah
GMP Lead Inspector & Trainer.
Drug factory inspection department



Agenda

1. GMP manufacturing environments
2. HVAC systems
3. HVAC design requirements





To answer the following questions:

- What is the best GMP manufacturing environment ?
- What kind of air grade and HVAC technology exist ?
- What do air filters have to do ?
- How are HVAC systems maintained ?
- What does qualification of HVAC systems include ?
- What is to be considered for risk assessment ?



1. GMP manufacturing environments
2. HVAC systems
3. HVAC design requirements

GMP MANUFACTURING ENVIRONMENTS



- The primary objective of pharmaceutical manufacturing site is to prevent contamination and cross-contamination of the product being manufacturing.

- The contamination comes from environment, materials or products and personnel
(5M = *men, machinery, material, method, milieu*).

- An ideal GMP "indoor environment" should prevent the contamination of product.

- An ideal GMP "indoor environment" should also facilitate the operator comfort, satisfaction and safety.

GMP MANUFACTURING ENVIRONMENTS



GMP MANUFACTURING ENVIRONMENT

- **PERSONNEL PROTECTION**
  - Prevent contact with dust
  - Prevent contact with fumes
  - Good comfort conditions
- **PRODUCT PROTECTION**
  - Protect from contamination
  - Protect from cross-contamination
  - Prevent contamination by staff
  - Correct conditions humidity, t°, light
- **ENVIRONMENT PROTECTION**
  - No dust discharge
  - No fumes discharge
  - No effluent discharge



GMP MANUFACTURING ENVIRONMENTS

Personnel

Validated processes

Procedures

Raw Materials

Equipment

Packing Materials

Premises

Environment

Factors contributing to quality products:

….

a failure of one of these factors will lead to sub-standard products.

GMP MANUFACTURING ENVIRONMENTS



For a GMP environment, the basic criteria to be considered should include:

- air filtration, air change rate or flushing rate, room pressure, location of air terminals (supply / return air), direction airflow, temperature, humidity, outside air conditions;
- building finishes, structure and lay-out;
- material flow, personnel flow;
- …..

GMP MANUFACTURING ENVIRONMENTS



- HVAC systems have to be designed and managed according to GEP and GMP.

- HVAC systems can have a direct impact on product quality (i.e. HVAC for clean rooms: GEP + GMP) or an indirect impact (i.e. general HVAC system: GEP).

- HVAC systems with a direct impact must be identified and documented in details and evaluated in relation to critical GMP parameters.



GMP MANUFACTURING ENVIRONMENTS



- GEP = Good Engineering Practices are defined as established engineering methods and standards that are applied throughout the lifecycle to deliver appropriate and cost-effective solutions.

- Generally the term is used to describe an engineering management system that is being applied in the engineering profession for delivering, operating and maintaining capital resources.

(from WHO glossary)



GMP MANUFACTURING ENVIRONMENTS

AHU system
(direct impact)

AHU

Critical
component
(direct impact)

HEPA

Aseptic
area

Chilled water system
(indirect impact)





Utilities: GMP direct Impact

Purified water
WFI
HVAC to clean rooms
Gasses for production
CIP/SIP
Environmental monitoring
Etc.

Utilities: GMP no direct Impact

Heating systems
Potable water
Fire systems
Effluent treatment
General HVAC
Lighting
Cooling water
Etc.

GMP MANUFACTURING ENVIRONMENTS

- GEPs are expected in a pharmaceutical industry (or in any industry….).
- cGMPs are mandatory in a pharmaceutical industry.

GEP + cGMP = good HVAC design and maintenance.





A good HVAC system means:

- Fitted for the intended purpose, reliable and economic to run;
- Designed taking into account GMP requirements as well as requirements for safety, ecology, … and country regulations;
- Designed, installed and maintained by skilled personnel;
- Supported by appropriate documentation (diagrams, as-built drawings, test reports, risk assessment, qualification, …).

GMP MANUFACTURING ENVIRONMENTS



Factors to take into account to design a HVAC system:

- Critical room parameters which can affect products (i.e. humidity, temperature);
- Process operations presenting a potential risk of contamination (i.e. air movement, particulate contamination, microbial contamination);
- Other potential sources of room contamination (equipment, interlocks, HVAC maintenance, personnel, failures of HVAC functions).



1. GMP manufacturing environments
2. HVAC systems
3. HVAC design requirements





Some definitions:

HVAC: Heating, Ventilation and Air Conditioning

« HVAC System » or « Ventilation System »?

- HVAC System includes sub-systems (chilled water, brine, steam, etc.).
- Ventilation system includes the air treatment components (AHU, ducts, flow controllers, etc.

BMS: Building Management System

- BMS: Building Management System (BMS) is a computer based control system installed in buildings that controls and monitors the building's mechanical and electrical equipment such as air handling and cooling plant systems, lighting, power systems, fire systems, and security systems

HVAC SYSTEMS



Air handling systems:

HVAC SYSTEMS



Overview of components

Silencer
Flow rate controller
Fan
Filter
Weather louvre
Control damper
Humidifier
Prefilter
Terminal filter
Production Room
Cooling coil with droplet separator
Heating coil

CPD

HVAC SYSTEMS COMPONENTS

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- Weather Louvre: to prevent insects, leaves, dirt and rain from entering;
- Silencer: to reduce noise caused by air circulation;
- Flow rate controller: automated adjustment of volume of air;
- Control damper: fixed adjustment of volume of air;
- Heating unit: to heat the air to the proper temperature;
- Cooling unit: to cool the air to the required temperature;
- Dehumidifier: to remove moisture from the air;
- Filters: to eliminate particle of pre-determined dimensions and / or microorganisms;
- Ducts: to transport the air.

HVAC SYSTEMS COMPONENTS



Failure possibilities with components:

- Flow rate controller: blocked;
- Control damper: poorly adjusted, bad pressure differential system;
- Humidifier: bad water / steam quality / poor drainage;
- Cooling battery: no elimination of condensed water / poor drainage;
- Filters: incorrect retention rate / damaged / badly installed;
- Ducts: inappropriate material / internal insulator leaking.

HVAC SYSTEMS







AHU with fan Variable Speed Controller

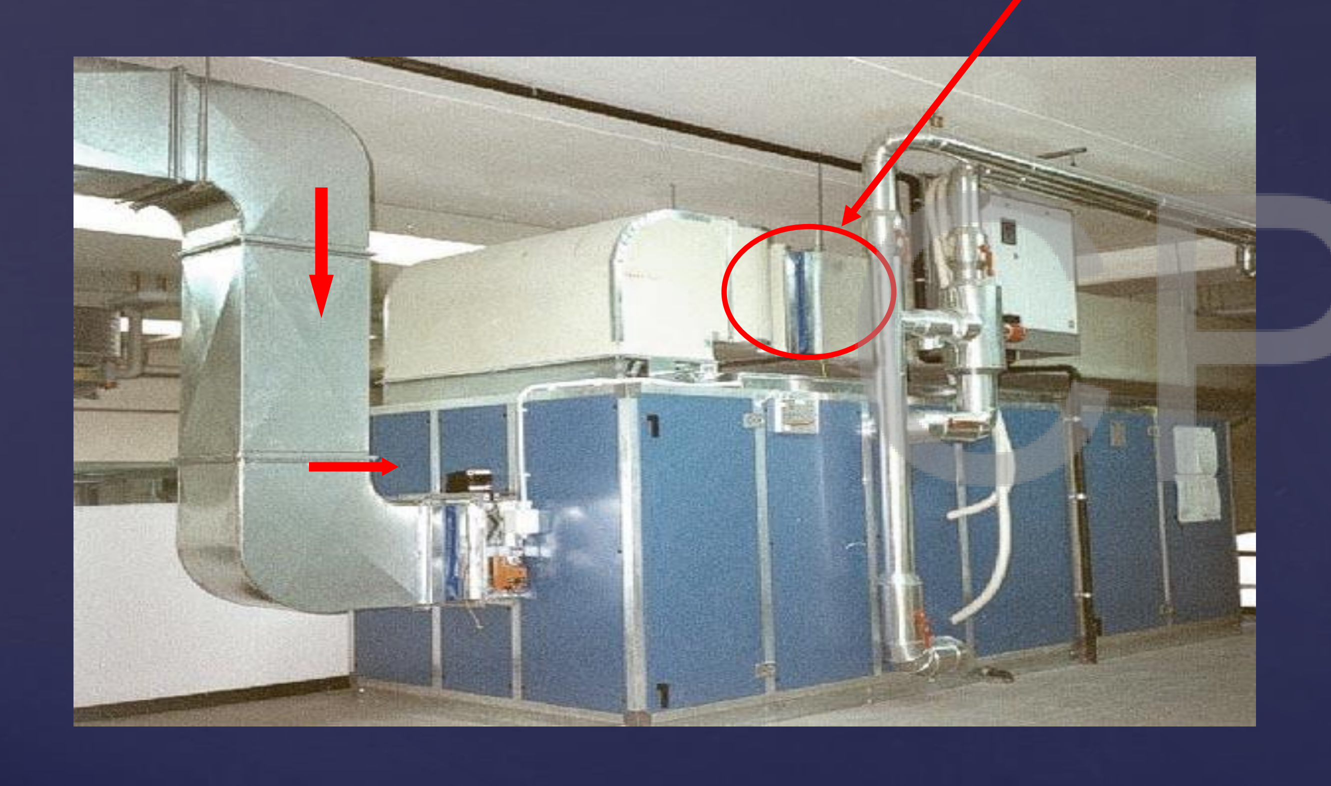
Air Handling Unit: fresh/make-up air is filtered through the outside air assembly (left) featuring easy-to-replace high efficiency pre-filters, which is ducted to packaged air conditioning units (right).

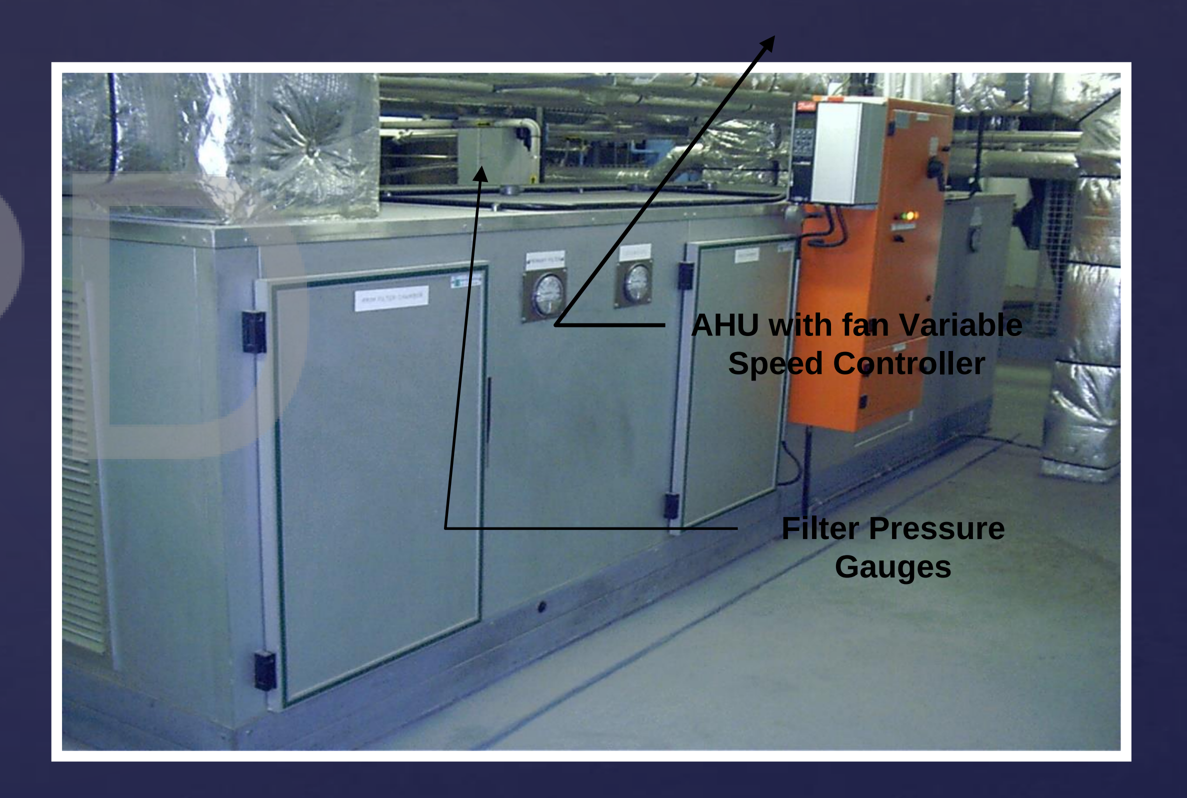
Dominant and seasonal wind direction should be taken into account when positioning exhaust and supply points.

HVAC SYSTEMS



Liquid column manometer





Air handling unit



1. GMP manufacturing environments
2. HVAC systems
3. HVAC design requirements





HVAC DESIGN REQUIREMENTS



Air types: fresh, supply, return, exhaust air

Fresh air (inlet / make-up air)

Supply air

Exhaust air (outlet)

Production Room

Return air (re-circulated)

CPD

3

HVAC DESIGN REQUIREMENTS

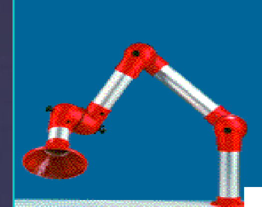


Characteristics of air handling system:

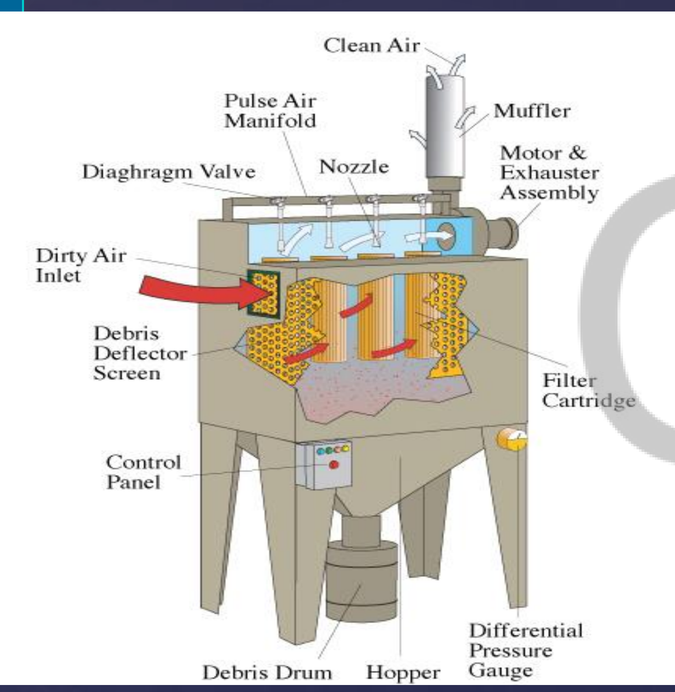
- 100% fresh air versus air re-circulation,
- Local extraction systems (local or central to be taken into account),
- Position return air system (low-wall air returns),
- Room grade or air cleanliness (air change, pressure differentials),
- Turbulent or uni-directional airflows (air flow patterns),
- Filters position (terminal filters).

HVAC SYSTEMS / DEDUSTING

3



Local air extraction



Dust collector (or dust control unit)





Central air extraction



HVAC DESIGN REQUIREMENTS



Outdoor air
Air Handler Unit (AHU)
Supply air
Exhaust air
Room
Infiltration
Exfiltration

Make-up air
Air Handler Unit (AHU)
Supply air
Re-circulated air
Room
Infiltration
Exhaust air
Exfiltration

There are two basic concepts of air delivery to pharmaceutical production facilities:
- fresh air

and
- re-circulation.

HVAC DESIGN REQUIREMENTS



Full fresh air system (100% outside air supply):

- It is used in a facility dealing with toxic products where re-circulation of air with contaminants should be avoided.
- The required degree of filtration of the exhaust air depends on the exhaust air contaminants and local environmental regulations (also valid for installations with air re-circulation).
- Energy recovery systems, via crossover plate heat exchangers and water coil heat exchangers, may be used in a multiproduct facilities.
- The potential for air leakage between the supply air and exhaust air should be prevented. The relative pressures between supply and exhaust air system should be such that the exhaust air system operates at a lower pressure than the supply system.

HVAC DESIGN REQUIREMENTS



Ventilation with 100% fresh air (no air re-circulation):

HVAC DESIGN REQUIREMENTS



Re-circulation system:

- It may be acceptable to use re-circulated air provided that HEPA filters are installed in the supply air stream to remove contaminants and prevent cross-contamination (HEPA filters should have a classification of H13).
- HEPA filters may not be required where the air-handling system is serving a single product facility and there is evidence that cross-contamination would not be possible.
- HEPA filters may be located in the air-handling unit or placed terminally.
- Air containing dust from highly toxic processes should never be re-circulated to the HVAC system.
- The proportions of “fresh/external air” and “recirculating air” can be fixed or variable according to the external temperature, to the number of people working.

HVAC DESIGN REQUIREMENTS



Ventilation with re-circulated air + make-up air:

Exhaust Air Handling Unit

make-up air

Central Air Handling Unit

Return air

CPD

HVAC DESIGN REQUIREMENTS



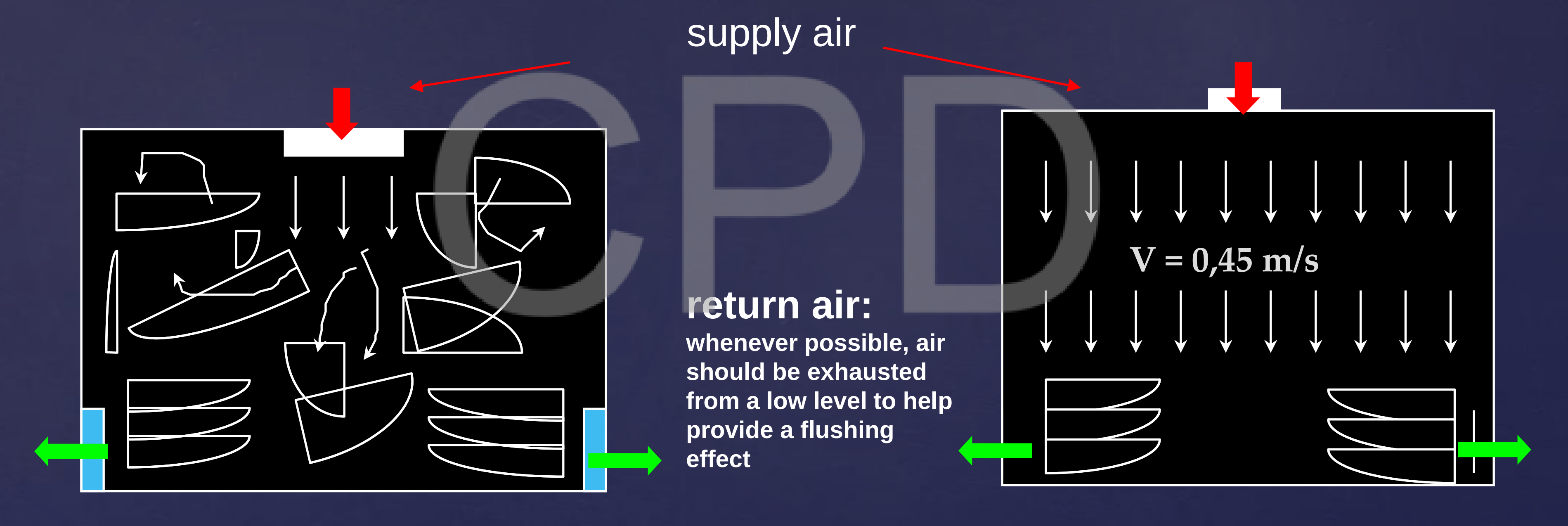
Control-system of the air volume flows: distinction between a constant or variable inlet and exhaust air current supply

VARIABLE AIR VOLUME FLOW	CONSTANT AIR VOLUME FLOW
Advantages: - low energy consumption / costs - more flexible system (i.e. in terms of changeable heat burdens) - external influences can be ruled out (i.e. by pressure regulation due to changing wind pressure)	**Advantages:** - simple design - steadily working system
Disadvantages: - more complex design - higher level of automation required	**Disadvantages:** - high energy consumption / costs - cannot react to changes

HVAC DESIGN REQUIREMENTS



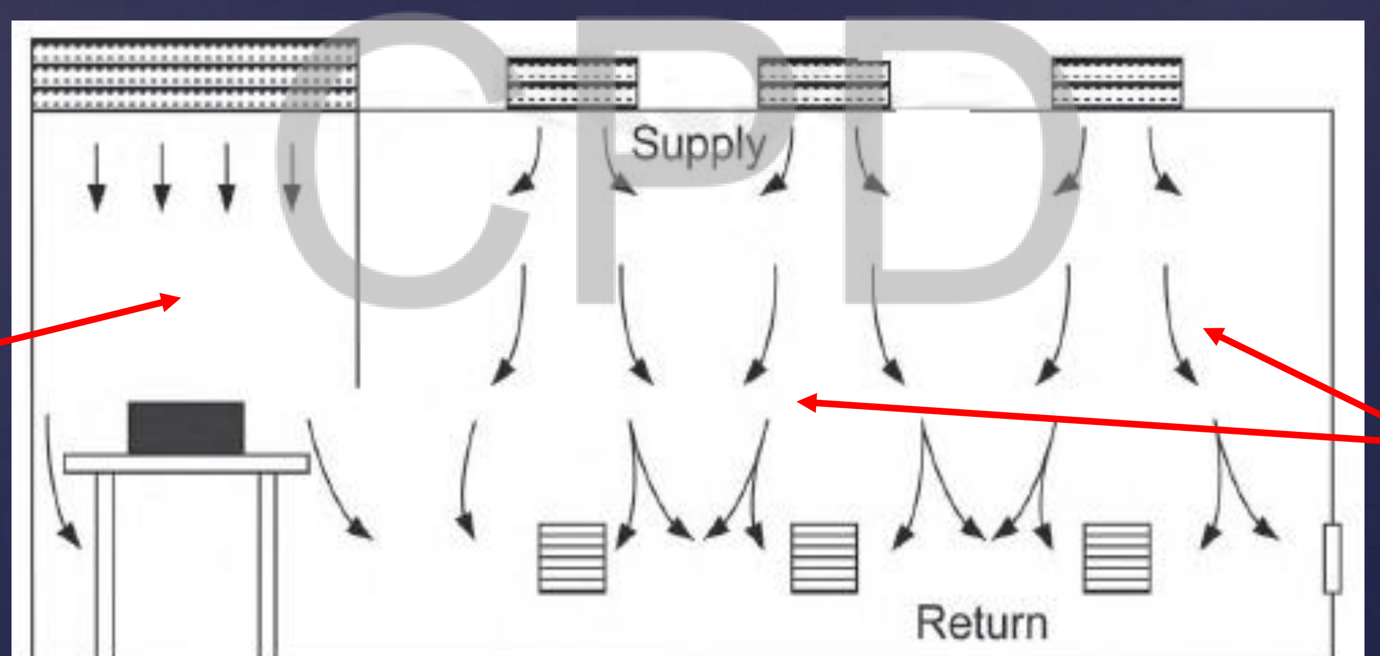
Air flow pattern: internal contaminants should be controlled by dilution or by displacement airflow



HVAC DESIGN REQUIREMENTS

Air flow pattern: mixed airflow

Laminar airflow



Turbulent airflow

HVAC DESIGN REQUIREMENTS



Uni-directional air flow:

Filtered air

Cabin booth (down-cross hood)

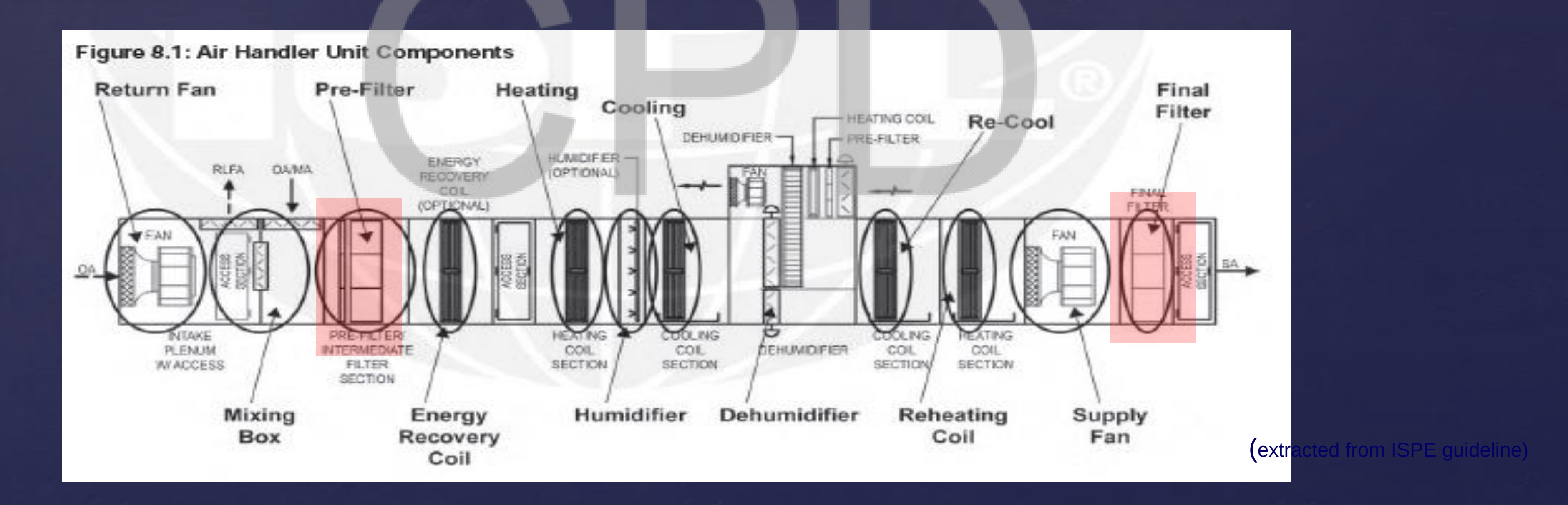


HVAC DESIGN REQUIREMENTS



Air handling unit and location of filters:

the required purity of the air can be achieved with effective cleaning of the external air or re-circulating air.
This requires correctly designed filter systems.



(extracted from ISPE guideline)

HVAC DESIGN REQUIREMENTS



Location of filters:

AHU with HEPA final filter

HEPA filter in terminal position

HEPA Filter

Production Room

HEPA Filter

Production Room

HVAC DESIGN REQUIREMENTS



Filter classes:

- Dust filters
  - Standard (EN 779 standard)
    - Coarse: $Dp > 10\ \mu m$ — G1 - G4
    - Fine: $1\ \mu m < Dp < 10\ \mu m$ — F5 - F9
  - Aerosol (EN 1822 Standard): $Dp < 1\ \mu m$
    - HEPA — H 11 – H 14
    - ULPA — U15- U16

EN 779 standard

EN 1822 Standard

HVAC design requirements



Table 5.3: Filter Comparison – Pre-filters

These comparisons of filter rating systems are only approximate as the test methods are different.

ASHRAE 52.2 MERV Composite Average Particle Size Efficiency, % in Size Range, µm			ASHRAE 52.2	EU type	EN 779
E1 – Range 1 0.30 – 1.0	E2 – Range 2 1.0 – 3.0	E3 – Range 3 3.0 – 10.0	MERV Designation	Designation	Designation
n/a	n/a	$E_3 < 20$	1	EU 1	G 1
n/a	n/a	$E_3 < 20$	2	EU 2	G 2
n/a	n/a	$E_3 < 20$	3	EU 2	G 2
n/a	n/a	$E_3 < 20$	4	EU 2	G 2
n/a	n/a	$20 \le E_3 < 35$	5	EU 3	G 3
n/a	n/a	$35 \le E_3 < 50$	6	EU 4	G 4
n/a	n/a	$50 \le E_3 < 70$	7	EU 4	G 4
n/a	n/a	$70 \le E_3$	8	EU 5	F 5
n/a	$E_2 < 50$	$85 \le E_3$	9	EU 5	F 5
n/a	$50 \le E_2 < 65$	$85 \le E_3$	10	EU 5	F 5
n/a	$65 \le E_2 < 80$	$85 \le E_3$	11	EU 6	F 6
n/a	$80 \le E_2$	$90 \le E_3$	12	EU 6	F 6
$E_1 < 75$	$90 \le E_2$	$90 \le E_3$	13	EU 7	F 7
$75 \le E_1 < 85$	$90 \le E_2$	$90 \le E_3$	14	EU 8	F 8
$85 \le E_1 < 95$	$90 \le E_2$	$90 \le E_3$	15	EU 9	F 9
$95 \le E_1$	$95 \le E_2$	$95 \le E_3$	16	EU 9	F 9
					EN 1822*
			16	EU 10	H10

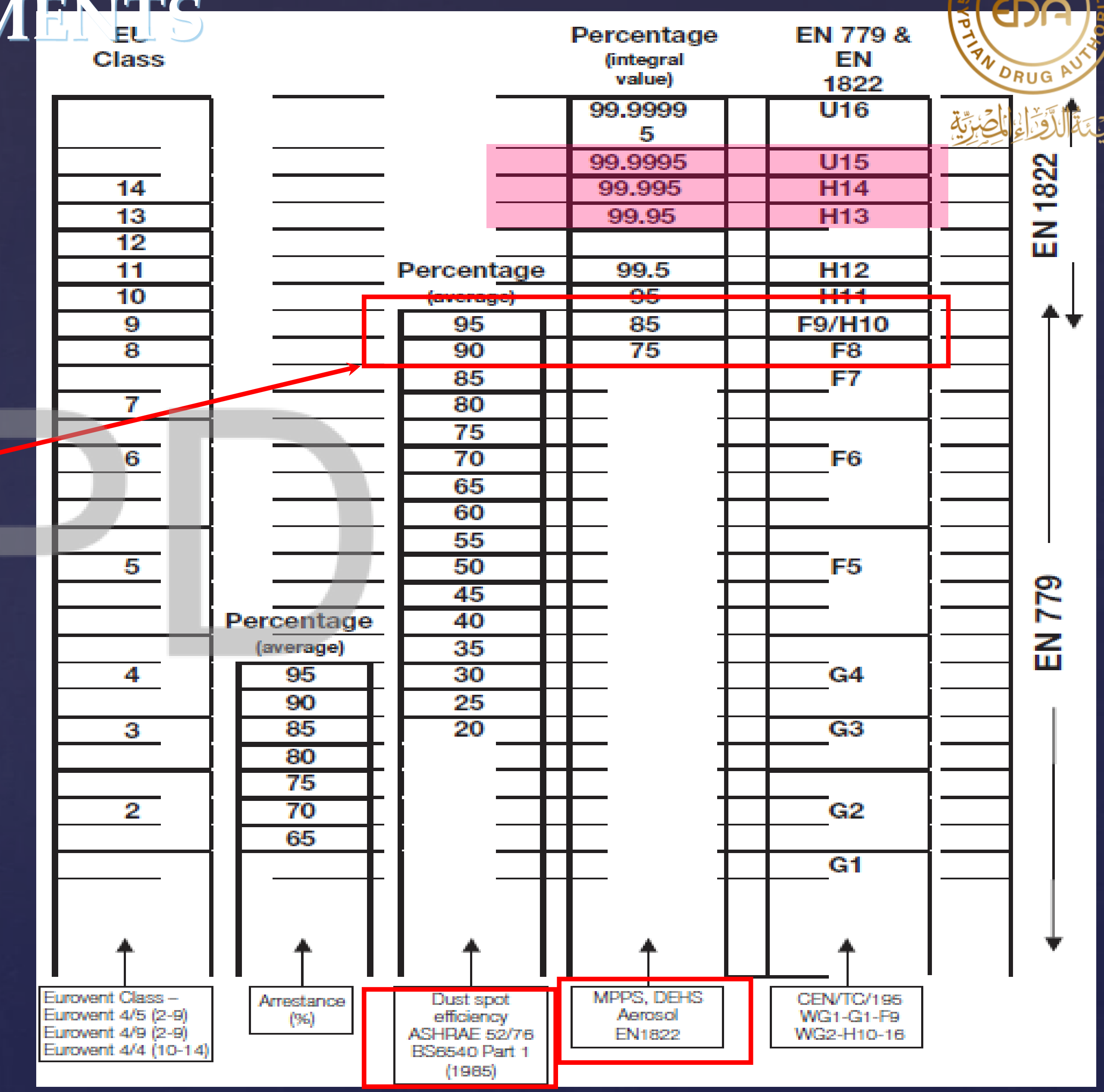
*All EN 1822 tests at MPPS   H = HEPA; U = ULPA

(by ISPE guideline)

HVAC DESIGN REQUIREMENTS

Filter classes:

they should always be linked to the standard test method because referring to actual filter efficiencies can be very misleading (as different test methods give results in a different value for the same filter) – *see comparison aside-*



EN European norm (euro norm)

EU European Union

HVAC DESIGN REQUIREMENTS



Table 5.4: Filter Comparisons – HEPA/ULPA

These comparisons of filter rating systems are only approximate as the test methods are different.

EU Type	EN 1822 HEPA/ULPA*		IEST Type (RP-CC001.4)	
Designation	Designation	Efficiency	Efficiency	Designation
EU 10	H10	85% @ MPPS		
EU 11	H11	95% @ MPPS		
EU 12	H12	99.5% @ MPPS		
			99.97% @ 0.3 mm**	A, B, E
EU 13	H13	99.95% @ MPPS	99.99% @ 0.3 mm**	C
EU 14	H14	99.995% @ MPPS	99.999% @ 0.3 mm**	D, K
	U15	99.9995% @ MPPS	99.999% @ 0.1 – 0.2 mm**	F
	U16	99.99995% @ MPPS	99.9999% @ 0.1 – 0.2 mm**	G
	U17	99.999995% @ MPPS		

*All EN 1822 tests at MPPS H = HEPA; U = ULPA

HEPAs = H10-H14, A, B, E, C, D, K; ULPA = U15-17, F, G

**All tested with thermally generated DOP aerosol (0.3 mm MMD; i.e., CMD is near MPPS). F, G and K type filters are tested at either 0.1 – 0.2 or 0.2 – 0.3 mm. K type filters are 99.995%.

(by ISPE guideline)

HVAC DESIGN REQUIREMENTS



(extracted from EN 1822-1)

Filter classes:

MPPS = minimum separation rate; the particle size with the highest penetration for a defined filter medium flow velocity is called the Most Penetration Particle Size (EN1822 uses single or discrete particle-counting instrument)

Table 1: Classification of HEPA and ULPA filters

Filter class	Overall value		Local value 1)2)	
	Efficiency (%)	Penetration (%)	Efficiency (%)	Penetration (%)
H 10	85	15	---	---
H 11	95	5	---	---
H 12	99,5	0,5	---	---
H 13	99,95	0,05	99,75	0,25
H 14	99,995	0,005	99,975	0,025
U 15	99,999 5	0,000 5	99,997 5	0,002 5
U 16	99,999 95	0,000 05	99,999 75	0,000 25
U 17	99,999 995	0,000 005	99,999 9	0,000 1

1) see 6.5.2 and prEN 1822-4
2) local values lower than those given in the table may be agreed between supplier and purchaser

Efficiency based on MPPS (Most Penetration Particle Size)

Overall efficiency: the efficiency, averaged over the whole superficial face area of a filter element under given operating conditions of the filter

Local efficiency: the efficiency, at a specific point of the filter element under given operating conditions of the filter

HVAC DESIGN REQUIREMENTS





Pocket filter (G3-G4)



Rigid pocket filter (F5-F9)



HEPA filter (H10-H14)



HVAC DESIGN REQUIREMENTS

Components of a HEPA filter:

Continuous sheet of filter medium
Filter frame
Filter sheet of randomly arranged fibres
Interception
Impact
Diffusion
Aluminium separator

Upstream Side
Media
Frame
Gasket
Airflow
Downstream Side



HVAC DESIGN REQUIREMENTS

Pressure Cascade:

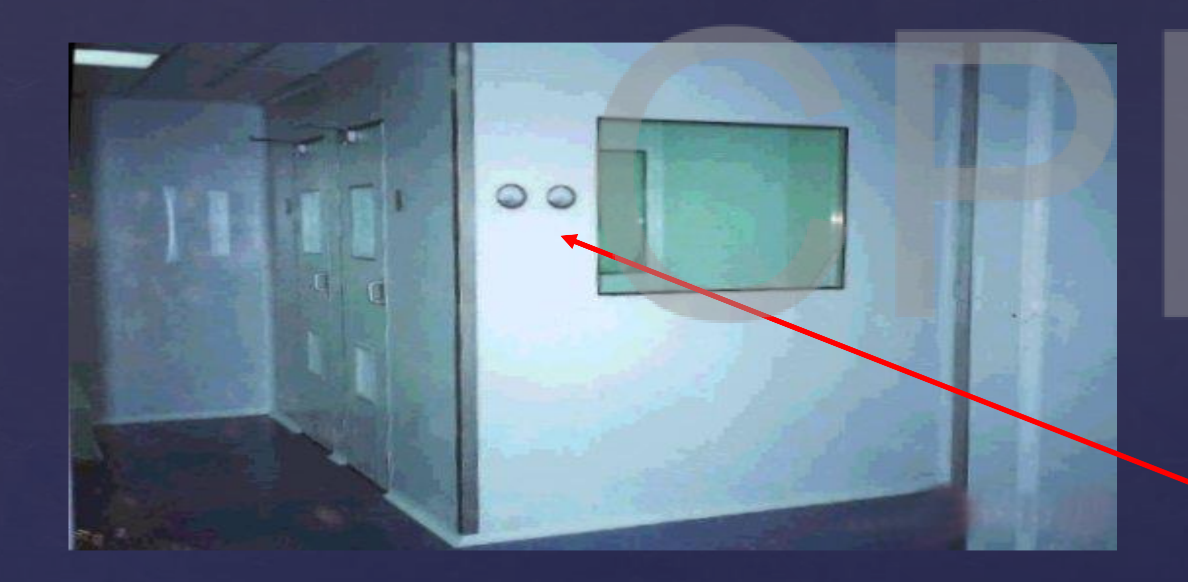
A process whereby air flows from the cleanest area, which is maintained at the highest pressure to a less clean area at a lower pressure in order to:

- prevent cross-contamination between areas;
- prevent ingress of contaminants from outside;
- separate areas of different cleanliness.

HVAC DESIGN REQUIREMENTS



The pressure differential over the doorway is measured with a magnehelic gauge or liquid manometer.





Permanently installed gauges: indication panel.

HVAC DESIGN REQUIREMENTS







Liquid column manometer
(also called “inclined manometer)

HVAC DESIGN REQUIREMENTS



Pressure Cascade: oral solid dosage plant OSD

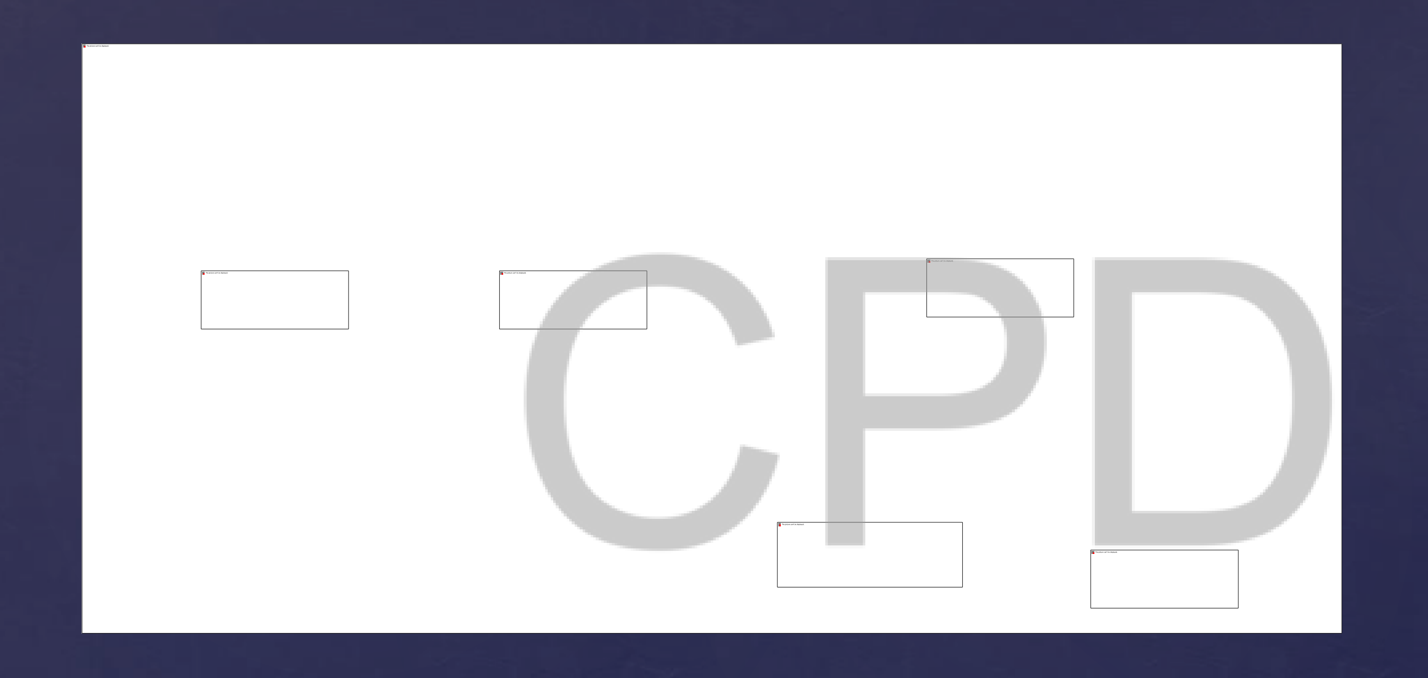
CPD

Apply a differential pressure between adjacent areas…..

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Pressure Cascade: oral solid dosage plant OSD

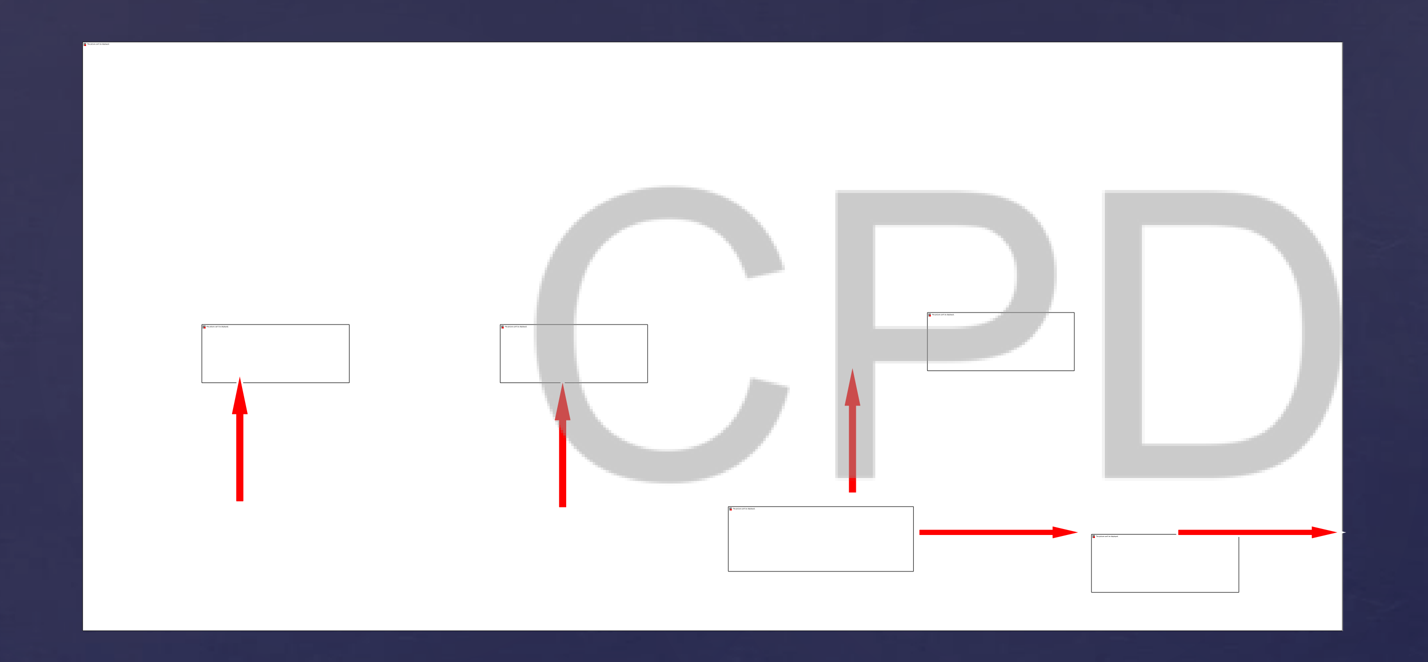


Doors should open to the high pressure side and be provided
with self closer.
Sliding doors are not recommended

HVAC DESIGN REQUIREMENTS



Pressure Cascade: oral solid dosage plant OSD



Doors should open to the high pressure side and be provided with self closer. Sliding doors are not recommended.

HVAC DESIGN REQUIREMENTS



The effect of room pressure tolerances in OSD plant

Tablets compr. 15 Pa ± 3 Pa | Tablets compr. 15 Pa ± 3 Pa | Encapsulation 15 Pa ± 3 Pa | Air lock 15 Pa | 30 Pa ± 3 Pa | Production corridor

Design condition (15 Pa differential)

Tablets compr. 12 Pa | Tablets compr. 12 Pa | Encapsulation 12 Pa | Air lock 12 Pa | 33 Pa | Production corridor

Maximum differential (21 Pa differential)

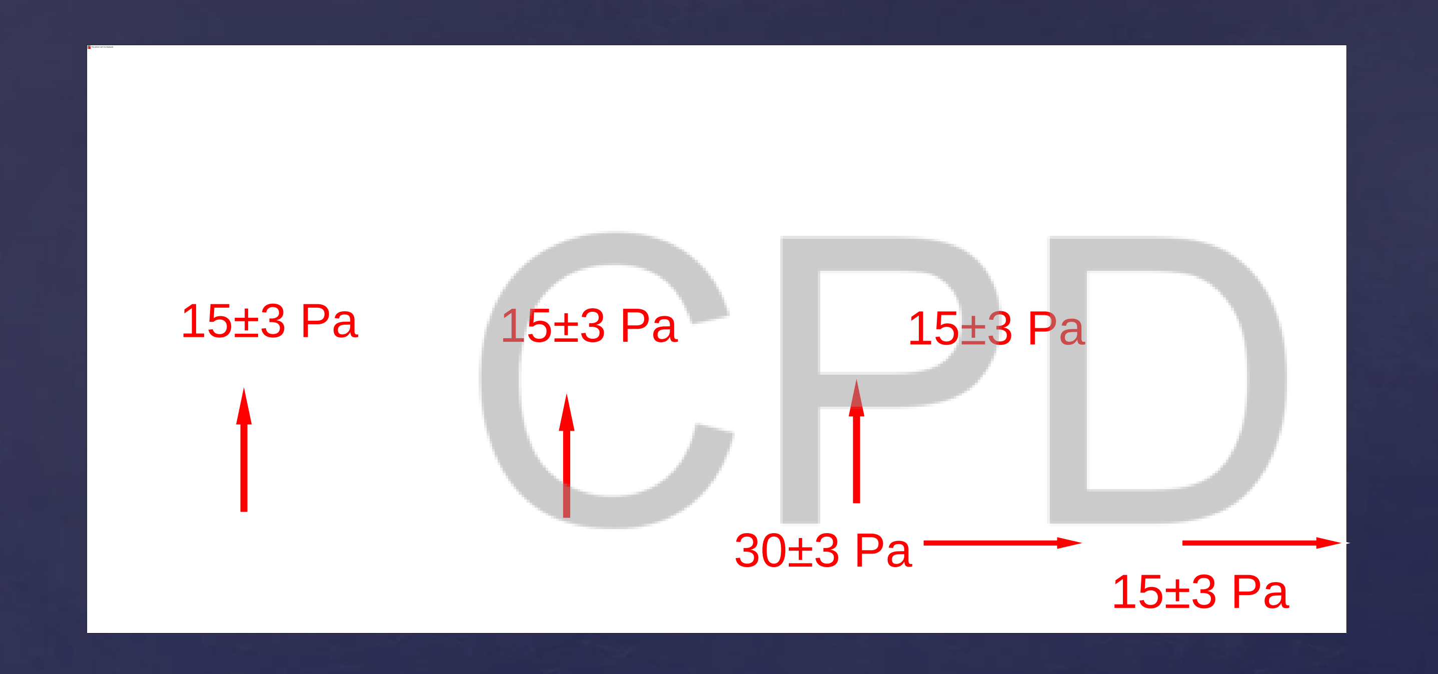
Tablets compr. 18 Pa | Tablets compr. 18 Pa | Encapsulation 18 Pa | Air lock 18 Pa | 27 Pa

Minimum differential (9 Pa differential)

The limits for the pressure differential between adjacent areas should be such that there is no risk of overlap, i.e. 5 Pa to 15 Pa in one room and 15 Pa to 30 Pa in an adjacent room, resulting in no pressure cascade, if the first room is at the maximum tolerance and the second room is at the minimum tolerance.



Pressure Cascade: oral solid dosage plant OSD



The pressure range should not interfere with the differential pressure of different areas.

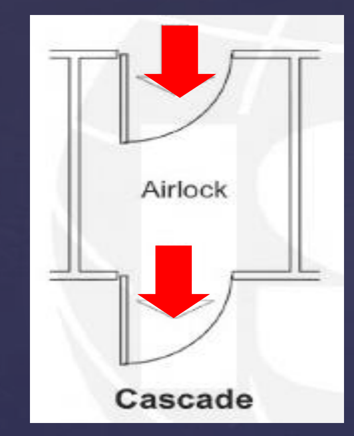
Worst case: 15+3=18 Pa & 30-3=27 Pa; Δp = 9 Pa

HVAC DESIGN REQUIREMENTS

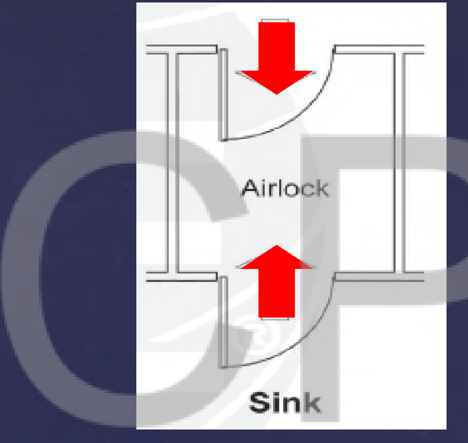


Pressure Cascade: airlocks

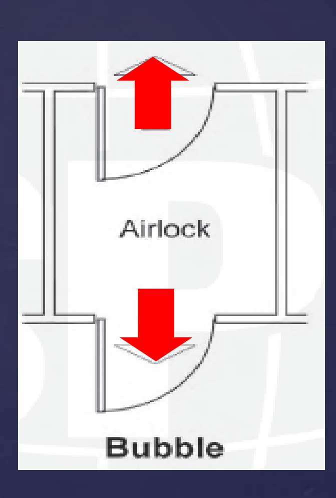
Three scenarios: cascade airlock, sink airlock and bubble airlock



High pressure on one side of the airlock and low pressure on the other.



Low pressure inside the airlock and high pressure on both outer sides.



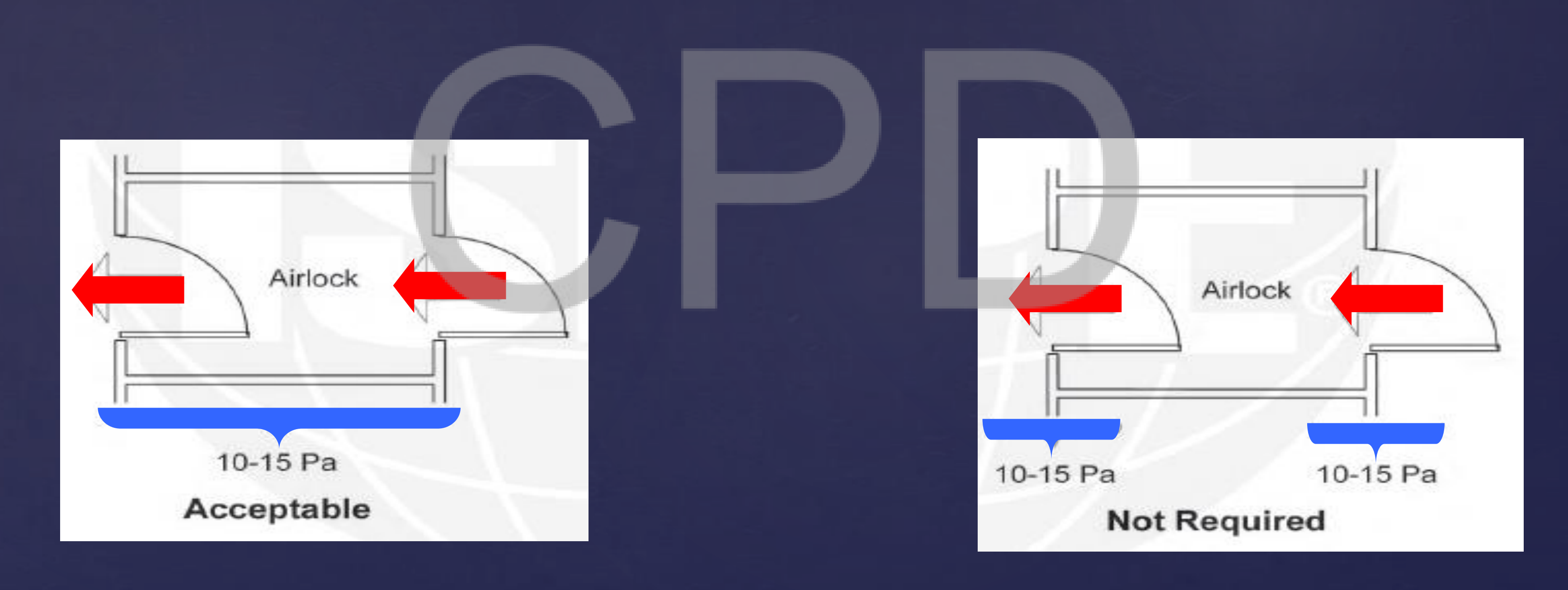
High pressure inside the airlock and low pressure on both outer sides.

HVAC DESIGN REQUIREMENTS



Pressure Cascade: airlocks

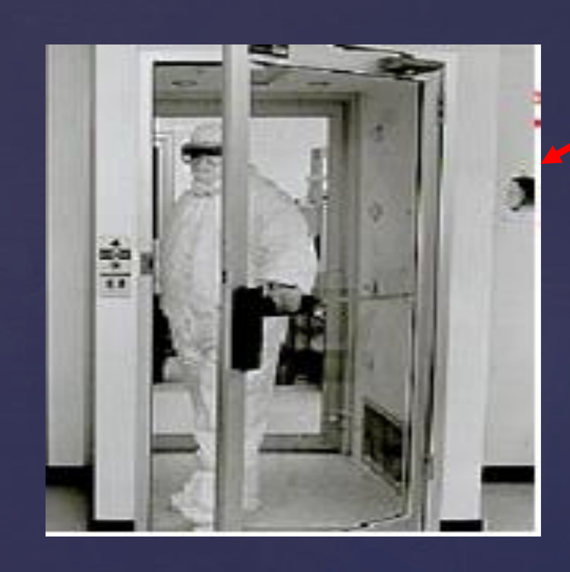
In case of cascade interlock, ISPE HVAC Guideline establishes that the pressure differentials is measured through the airlock and not through the single doors.



HVAC DESIGN REQUIREMENTS



Interlocks for personnel and materials



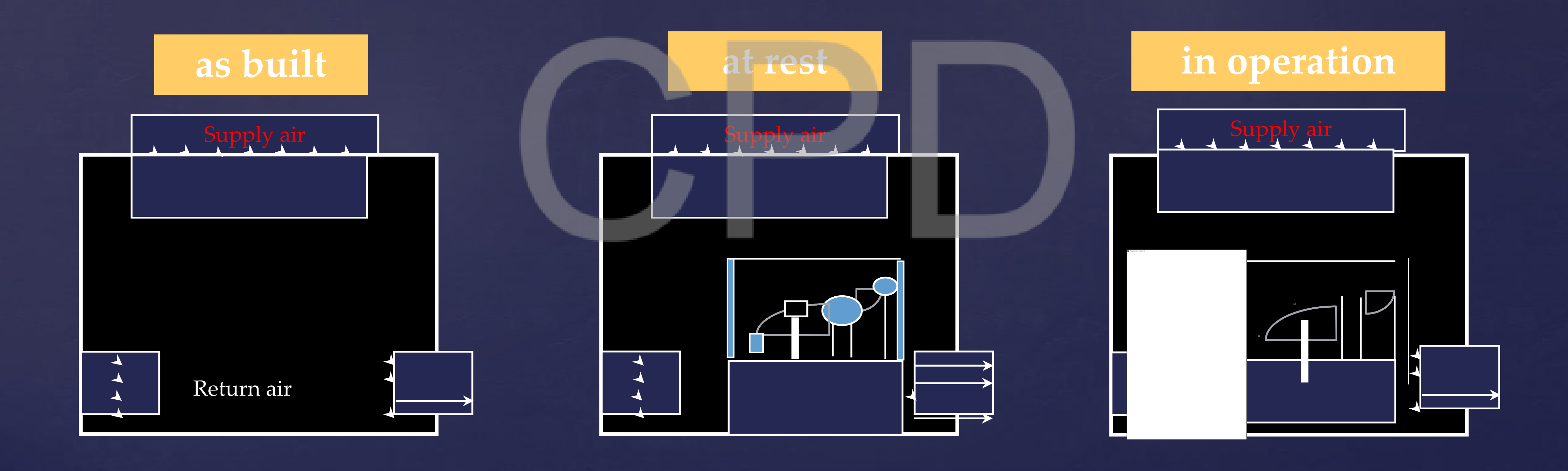


An airlock should not be used for communication

HVAC DESIGN REQUIREMENTS

Environment:

in **classifying** (qualifying) the environment, the manufacturer should state whether this is achieved under as-built, at rest or operational conditions.



HVAC DESIGN REQUIREMENTS



As built: condition where the installation is complete with all services connected and functioning but with no production equipment, materials or personnel present.

At rest / in operation: condition where the installation is complete with equipment installed and operating in a manner agreed upon the customer and supplier, but with no personnel present / and with personnel present.

HVAC DESIGN REQUIREMENTS



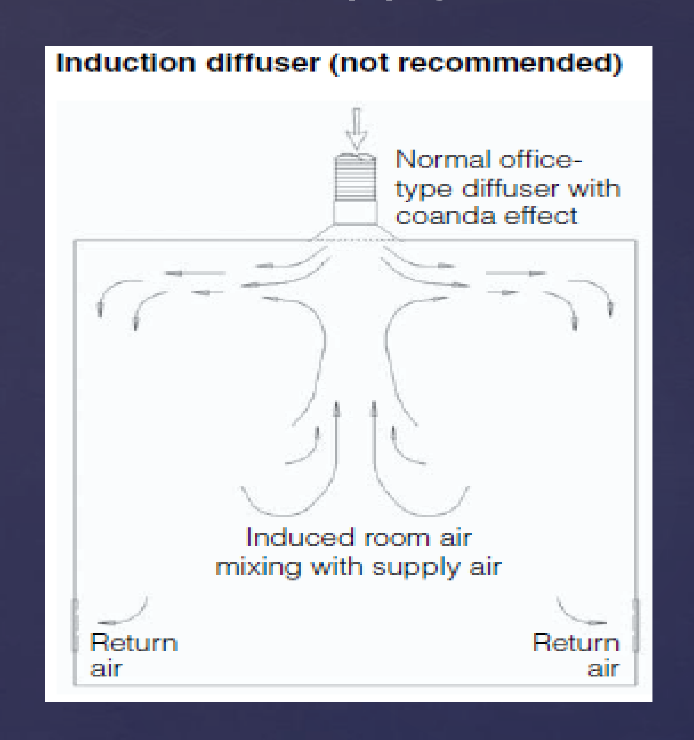
Supply air diffusers: the high induction type (i.e. those for office-type air conditioning) should not be used in clean areas.
They should be of non-induction type, introducing air with the least amount of induction so as to maximize the flushing effect.

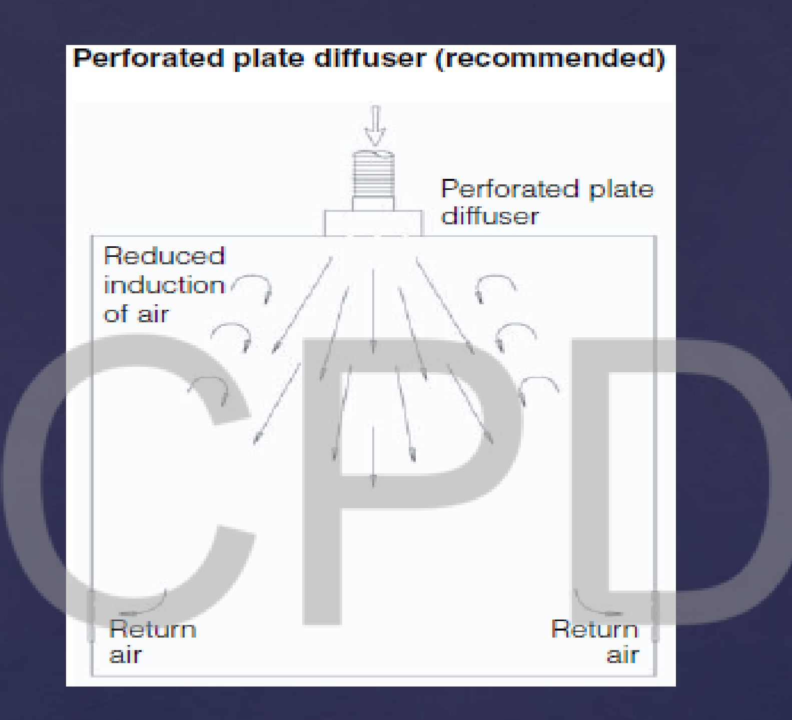
HVAC DESIGN REQUIREMENTS



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Supply air diffusers:

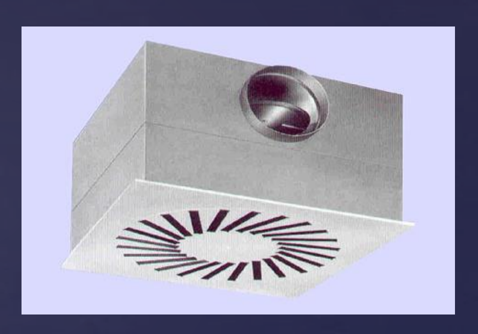






Coandă effect is the tendency of a fluid jet to be attracted to a nearby surface

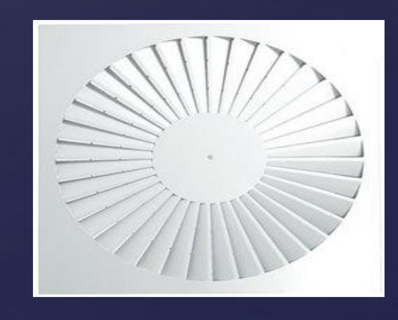
HVAC DESIGN REQUIREMENTS



Supply air diffusers:







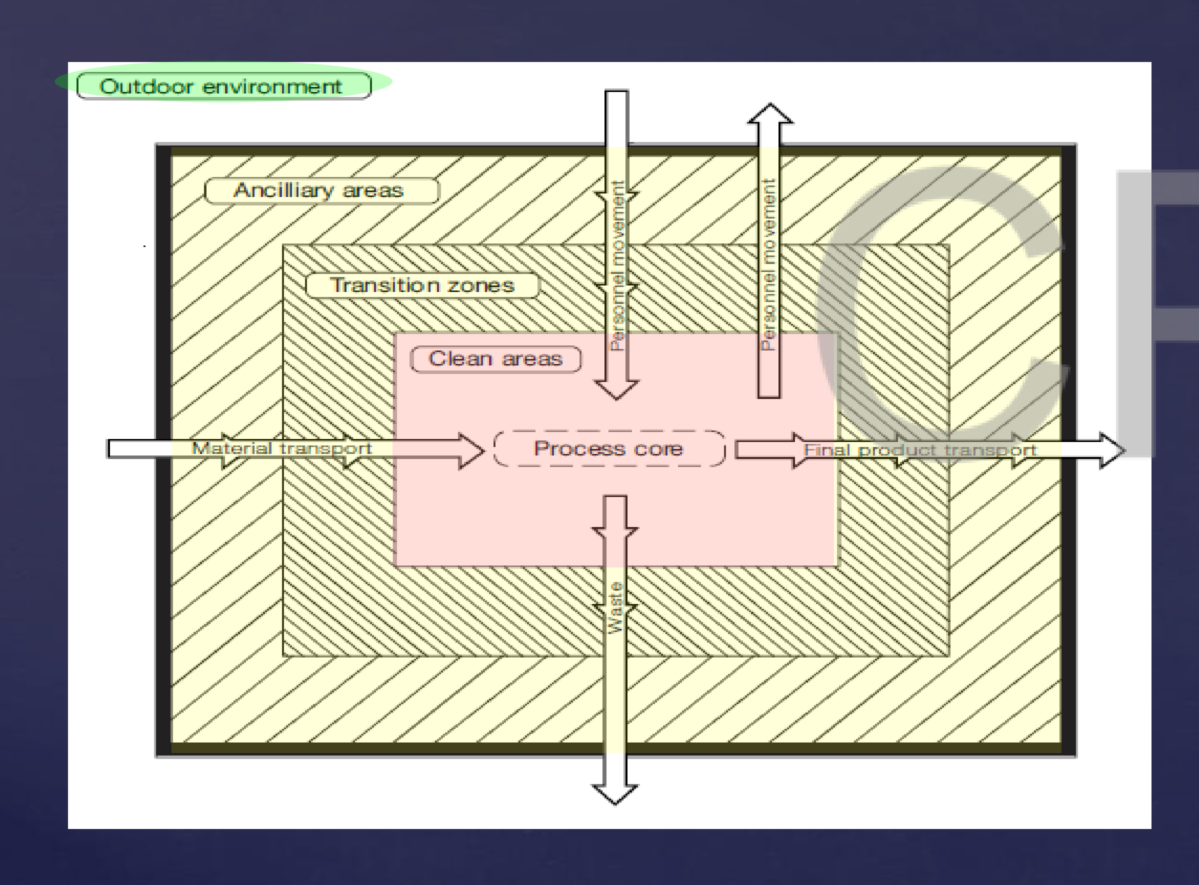
Induction diffuser

Perforated plate diffuser

Swirl diffuser

HVAC DESIGN REQUIREMENTS

Shell-like containment control concept: it improves protection from external contaminants:



The process core is regarded as the most controlled clean area which is protected by clean areas of a lower classification (i.e. Δp, clean grades, environment monitoring).

HVAC DESIGN REQUIREMENTS



What is a clean room?

A clean room is a closed room supplied with “filtered (purified) air” in which the particulate and bacterial contamination concentration is below a specified level.

Special guidelines are in place for the room air technology, room furnishings, process equipment, personnel and the procedures.

Pharmaceutical products can be produced in “clean rooms” of different grades, depending on the type of product to be manufactured.

HVAC DESIGN REQUIREMENTS



4.3 For the manufacture of sterile pharmaceutical preparations, four grades of clean areas are distinguished as follows:

- *grade A*: The local zone for high-risk operations, e.g. filling and making aseptic connections. Normally such conditions are achieved by using a unidirectional airflow workstation. Unidirectional airflow systems should provide a homogeneous air speed of 0.36–0.54 m/s (guidance value) at a defined test position 15–30 cm below the terminal filter or air distributor system. The velocity at working level should not be less than 0.36 m/s. The uniformity and effectiveness of the unidirectional airflow should be demonstrated by undertaking airflow visualization tests;
- *grade B*: In aseptic preparation and filling, this is the background environment for the grade A zone;
- *grades C and D*: Clean areas for carrying out less critical stages in the manufacture of sterile products or carrying out activities during which the product is not directly exposed (i.e. aseptic connection with aseptic connectors and operations in a closed system).

annex 4)

HVAC DESIGN REQUIREMENTS

Operations in clean rooms

Grade	Examples of operations for terminally sterilised products
A	Filling of products, when unusually at risk.
C	Preparation of solutions, when unusually at risk. Filling of products
D	Preparation of solutions and components for subsequent filling.

Grade	Examples of operations for aseptic preparations.
A	Aseptic preparation and filling.
C	Preparation of solutions to be filtered
D	Handling of components after washing

HVAC DESIGN REQUIREMENTS



Maximum permitted airborne particle concentration

	Maximum permitted number of particles per m³ greater than or equal to the tabulated size			
	At rest[a]		In operation[b]	
Grade	0.5 µm	5.0µm	0.5 µm	5.0µm
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not defined	Not defined

[a] The "at rest" state is the condition where the installation is complete with equipment installed and operating in a manner agreed upon by the customer and supplier, but with no personnel present.

[b] The "in operation" state is the condition where the installation is functioning in the defined operating mode and the specified number of personnel is present. The areas and their associated environmental control systems should be designed to achieve both the "at rest" and "in operation" states.

(WHO guideline)

HVAC DESIGN REQUIREMENTS



Recommended limits for microbial contamination[a]

Grade	Air sample (CFU/m³)	Settle plates (diameter 90 mm) (CFU/4 hours)[b]	Contact plates (diameter 55 mm) (CFU/plate)	Glove print (5 fingers) (CFU/glove)
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	–
D	200	100	50	–

CFU, colony-forming units.

[a] These are average values.

[b] Individual settle plates may be exposed for less than 4 hours.

(WHO guideline)

HVAC DESIGN REQUIREMENTS / DE-HUMIDIFATION



Reactivation Air

Wet Air

Hot Air

Cool Air

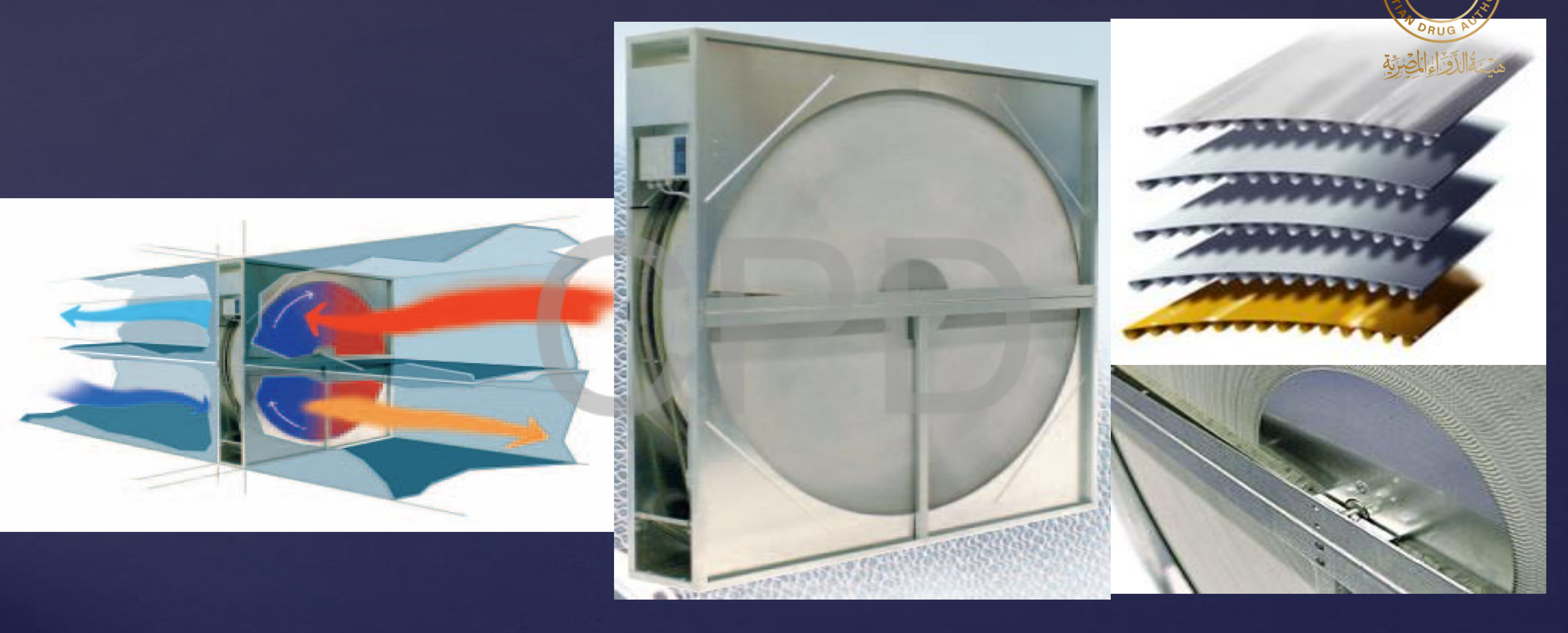
Dry Air

Process Air

Drive Motor

Lithium Chloride
as dehumidifier

HVAC DESIGN REQUIREMENTS
ENERGY RECOVERY



De-humidification

HVAC DESIGN REQUIREMENTS

The materials and personnel have to access into clean areas through air locks: “material air lock (or pass box) ” and “changing rooms (or gowning rooms)”.

Air locks must always fulfill the relevant requirements of the higher zone in terms of minimizing microbiological and particulate contamination.

Air locks should have the same cleanliness grade as the work area.

Only one door can be opened at a time.

Ventilation and pressure differential are required.

Cupboards used for the storage of clothes should be ventilated.

HVAC DESIGN REQUIREMENTS

A **personnel lock** is generally divided by a step-over-bench (or sit-over bench) that divides the areas corresponding to the adjacent cleanliness grades.

The design for personnel entering in a grade B class is:

- air lock in cleanliness grade non classified / D;
- air lock in cleanliness grade D / C;
- air lock in cleanliness grade C / B.

The materials entering a high cleanliness grade via a **material air-lock** must be cleaned and disinfected appropriately.

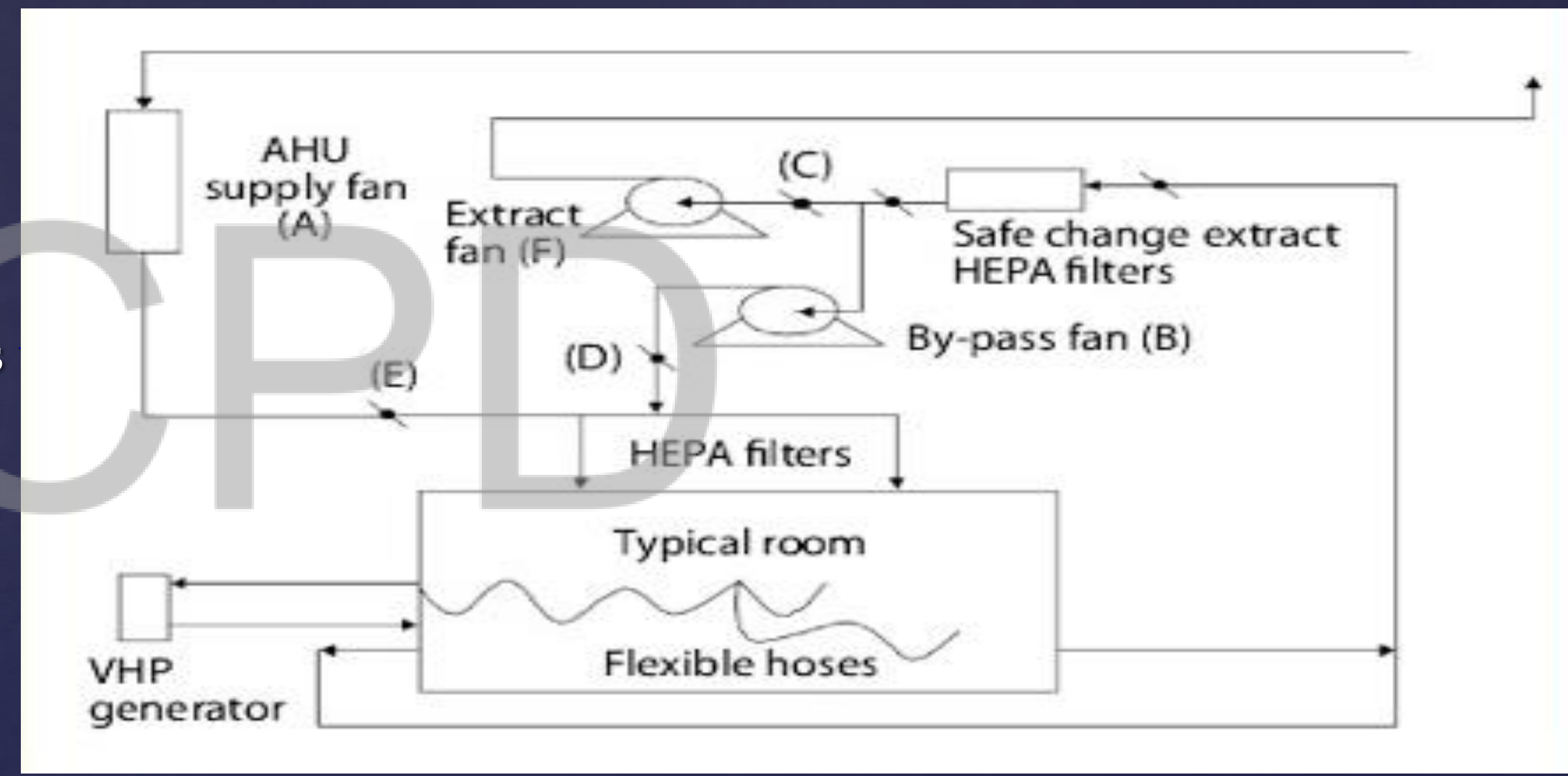
A residence time in the lock following the disinfection has to be established (validation should take into account the clean-up period).

Material airlocks to A/B, C must be monitored

HVAC CONCEPT:DECONTAMINATION



Possibility to decontaminate filters



COMPUTERIZED SYSTEMS
BUILDING AUTOMATION SYSTEM



A dedicated building automation system (BAS) shall be installed for the facilities, to cover e.g. the following technical, non-GMP functions:

- Control of air handling units
- Control of building utilities (e.g. chilled water, heating water, black steam, etc.)
- Fire alarm system

The BAS shall be designed as a system which is not GMP relevant, if possible.
This requires a proper definition of the system boundaries between the BAS and the GMP monitoring system (GMS) described below.
The boundary definition should be verified then by methodical (risk) assessment to avoid unwanted overlaps between the BAS and the GMS (in terms of GMP relevance).
If constructed as a non-GMP system, the BAS does not require qualification and validation.
In this case, the BAS shall be designed and installed following good engineering practices and shall be commissioned then.
The BAS shall be operated from a computer terminal located in a central control room.

COMPUTERIZED SYSTEMS
GMP MONITORING SYSTEM (GMS)



A dedicated and independent GMP monitoring system (GMS) shall be installed for the facilities
to cover e.g. the following GMP relevant functions:

- Monitoring and alerting of clean room parameters (temperature, relative humidity and differential pressure)
- Monitoring and alerting of UAF / LAF parameters (particle concentration and air speed)
- Access control
- VHP fumigation cycle control

The GMS is GMP relevant and has to be fully qualified and validated therefore.

The GMS shall be designed, programmed and installed according to the requirements described in GAMP 5 and shall comply with the requirements for electronic records and signatures as outlined in EudraLex Volume 4, Annex 11.

The GMS shall be operated from computer terminals located in a central control room.

Local alarms will be installed where necessary.



CPD

Thank you





CENTER FOR **CONTINUING PROFESSIONAL DEVELOPMENT**

مركز التطوير المهني المستمر





HVAC SYSTEMS, QUALIFICATION AND INSPECTIONS
Part 2

CPD

Dr. Mohamed Salah
GMP Lead Inspector.
Drug factory inspection department



Agenda

CPD

1. HVAC qualification, risk assessment
2. Inspecting HVAC

HVAC QUALIFICATION



- The qualification of the HVAC system should be described in a validation master plan.
- Stages of the qualification of the HVAC system should include DQ, IQ, OQ and PQ.
- Any parameter that may affect the quality of the pharmaceutical product should be considered as a critical parameter.
- All critical parameters should be included in the qualification process:
  - i.e. the humidity of the room where the product is exposed should be considered a critical parameter when a humidity-sensitive product is being manufactured. Thus the humidity sensors should be qualified;
  - i.e. a room cleanliness classification is a critical parameter and therefore the room air change rates and HEPA filters should be critical parameters and require qualification.

HVAC QUALIFICATION



- DQ: design of the system according to URS and risk assessment

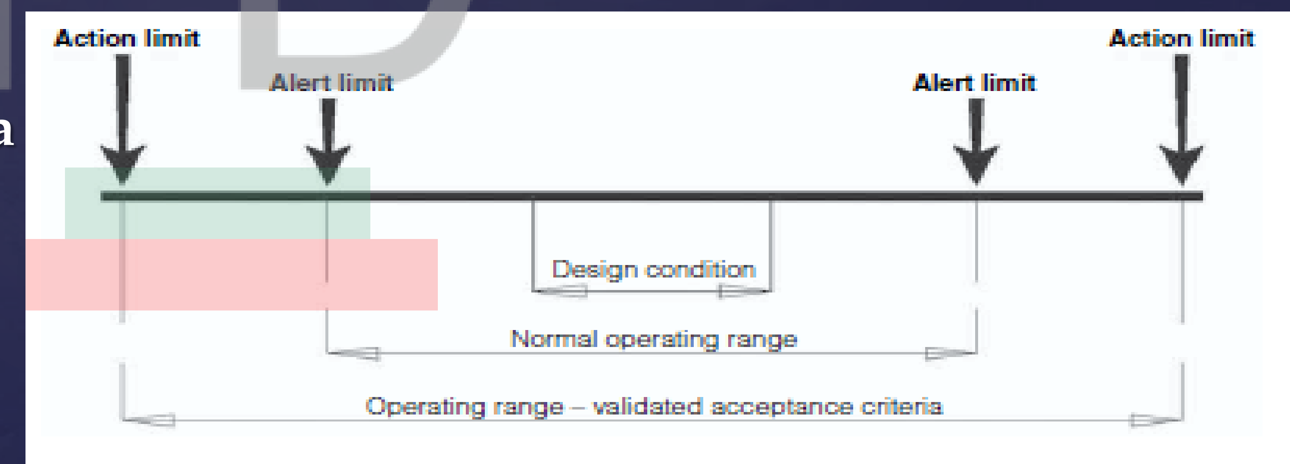
  (e.g. components, type of air treatment needed, materials of construction).
- IQ: verification of installed components; it is a static verification

  (e.g. relevant components, ducting, filters, controls, monitors, sensors etc.) / includes calibration where relevant.
- OQ: confirm HVAC is well designed and is working in "at rest conditions" – no personnel - (it has to be done prior the room qualification).
- PQ: confirm HVAC is working in operating condition (with personnel).
- Periodical re-qualification of parameters should be done at regular intervals (i.e. annually).
- Re-qualification should also be done when any change, which could affect system performance, takes place.

HVAC QUALIFICATION



- Non-critical system and components should be subject to GEP and may not necessarily require classification.
- Acceptance criteria and limits should be defined during the design stage.
- The manufacturer should define design conditions, normal operating ranges, operating ranges and alert and action limits.
- The relationship between design conditions operating range and qualified acceptance criteria



HVAC QUALIFICATION



Some of the typical HVAC system parameters that should be qualified may include:

- temperature (19-25 °C),
- relative humidity (40-65 % RH),
- supply air quantities for all diffusers,
- return air or exhaust air quantities,
- room air change rates (20 ac / hour is generally accepted for controlled areas),
- room pressures (pressure differential of 10-15 Pa as guidance value between different classes),
- room airflow patterns (smoke studies),
- unidirectional airflow velocities (range of 0.36-0.54 m/s at the working position in open clean room applications is given as guidance value),
- HEPA filter penetration tests (> 0,01 % leak; upstream concentration: 20 µg/l or 20 mg/m^3),
- room particle counts,
- room recovery (the particle limits given in the table for "at rest" state should be achieved after a short "clean up" period of 15-20 minutes – guidance value),
- microbiological air and surface counts (where appropriate),
- warning / alarm systems, where applicable.

4.25 Cleanroom and clean air equipment qualification is the overall process of confirming the level of compliance of a classified cleanroom or clean air equipment. As part of the qualification requirements, the qualification of cleanrooms and clean air equipment should include (where relevant to the design and operation of the installation):

i. installed filter leakage test and filter integrity testing
ii. airflow tests – volume and velocity
iii. air pressure differential test
iv. airflow direction test and air flow visualization test
v. microbial airborne and surface contamination test
vi. temperature measurement test
vii. relative humidity test
viii. recovery test
ix. containment leakage test.

Reference for the qualification of the cleanrooms and clean air equipment can be found in the *WHO Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products*[4] and ISO 14644 series of standards.



- Where routine or periodic revalidation is done, the frequency should be established based on, for example, risk, the type of facility, the level of product protection necessary, performance of the system and the extent of routine ongoing monitoring activities.
- Any change to the HVAC system should be handled according to a change control procedure. The extent of qualification or requalification should be decided based on the scope and impact of the change.

HVAC RE-QUALIFICATION



Part A: schedule of tests to demonstrate compliance (for reference purposes only)

Schedule of tests to demonstrate continuing compliance

Test parameter	Clean room class	Max. time interval	Test procedure
Particle count test (Verification of cleanliness)	All classes	6 months	Dust particle counts to be carried out and printouts of results produced. No. of readings and positions of tests to be in accordance with ISO 14644-1 Annex B
Air pressure difference (To verify absence of cross-contamination)	All classes	12 months	Log of pressure differential readings to be produced or critical plants should be logged daily, preferably continuously. A 15 Pa pressure differential between different zones is recommended. In accordance with ISO 14644-3 Annex B5*
Airflow volume (To verify air change rates)	All classes	12 months	Airflow readings for supply air and return air grilles to be measured and air change rates to be calculated. In accordance with ISO 14644-3 Annex B13*
Airflow velocity (To verify laminar flow or containment conditions)	All Classes	12 Months	Air velocities for containment systems and laminar flow protection systems to be measured. In accordance with ISO 14644-3 Annex B4*

Guidance values for schedule of tests to demonstrate continuous compliance

HVAC RE-QUALIFICATION



Part B: recommended optional strategic tests (ISO 14644)

Schedule of tests to demonstrate continuing compliance

Test parameter	Clean room class	Max. time interval	Test procedure
Filter leakage tests (To verify filter integrity)	All classes	24 months	Filter penetration tests to be carried out by a recognized authority to demonstrate filter media and filter seal integrity. Only required on HEPA filters. In accordance with ISO 14644-3 Annex B6*
Containment leakage (To verify absence of cross-contamination)	All classes	24 months	Demonstrate that contaminant is maintained within a room by means of: • airflow direction smoke tests • room air pressures. In accordance with ISO 14644-3 Annex B4*
Recovery (To verify clean-up time)	All classes	24 months	Test to establish time that a clean room takes to return from a contaminated condition to the specified clean room condition. This should not take more than 15 min. In accordance with ISO 14644-3 Annex B13*
Airflow visualization (To verify required airflow patterns)	All classes	24 months	Tests to demonstrate airflows: • from clean to dirty areas • do not cause cross-contamination • uniformly from laminar flow units. Demonstrated by actual or video-taped smoke tests. In accordance with ISO 14644-3 Annex B7*

Guidance values for schedule of tests to demonstrate continuous compliance

HVAC QUALIFICATION



- Qualification and re-qualification results have to be recorded and presented in report
- Traceability has to be available; e.g. devices and standards used, calibration records, test conditions

HVAC QUALIFICATION OQ / PQ



Tests to be performed:

- Filter pressure drop or differential pressure on filters.
- Differential pressure between rooms.
- Determination of air flow velocity.
- Measurement of air volume and uniformity – air exchange rate -.
- Determination of airflow patterns.
- Filter installation leak test.
- Determination of the recovery time.
- Determination of room classification (airborne particle count).
- Temperature / humidity level and uniformity test.

HVAC QUALIFICATION OQ / PQ



<u>Filter pressure drop</u> or differential pressure on filters (upstream / downstream):

- to detect initial defects of filters or when filter has been replaced,
- to connect the two probes of the gauge to the upstream side of the HEPA or ULPA filter and to the downstream side,
- record the measured differential pressure,
- the filter pressure drop should be not more than 50% greater than the initial value established by the filter supplier (value of clean-filter pressure drop).

HVAC QUALIFICATION OQ / PQ



Differential pressure between rooms:

- this test consists in measuring with a calibrated manometer the differential pressure existing between the inside of a (clean) room and the surrounding areas as defined in the specifications,
- this determination should be made under various operational conditions (such as opening of doors, etc.) to identify situations when the pressure differential cannot be met and as a consequence the product may be at risk.

B.1.2 Procedure for air pressure difference test

It is recommended that the following items are confirmed before starting the measurement of differential pressure between rooms or between rooms and outside areas:

— values and acceptable range of differential pressure between rooms should be defined;

— supply air volume and installation balancing are within specifications;

— cleanroom components that could impact the differential pressure between rooms such as doors, windows, pass through, etc. should be closed. Permanent openings should be kept open during the test;

— the air-conditioning system has been operated and the conditions have been stabilized.

HVAC QUALIFICATION OQ / PQ



Determination of air flow velocity:

- this test is used to determine average airflow velocity and uniformity of velocity within a clean room, clean zone or unidirectional flow work zone,
- in case of non-unidirectional airflow cleanliness areas, the measurement of airflow volumes is preferred ,
- the area is divided in grids and the airflow velocity is measured, using an anemometer, at a distance of 15-30 cm from the supply source (WHO) or at the working level (EU),
- the acceptance criteria are 0.45 ± 0.09 m/sec (EU).
  The maximum relative standard has to be not more than 15-20% when using the mean value of velocity.

B.2.2.2 Supply airflow velocity

The airflow velocity should be measured at approximately 150 mm to 300mm from the filter face or entry plane.

The number of measuring points (grid cells) is highly dependent upon the instrumentation used to perform the measurements and the design of the installed filter cell. The minimum number of measuring points (grid cells) should be determined by the following equation:

$$N = \sqrt{10 \times A}$$

where

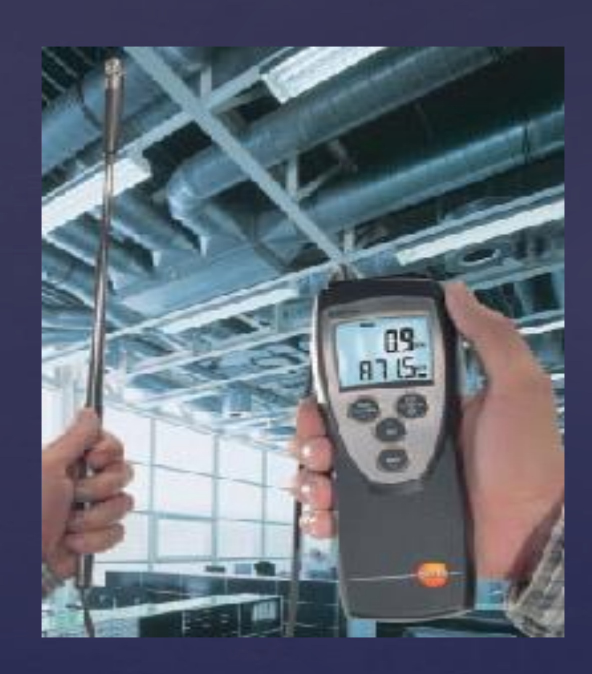
N is the minimum number of measuring points (grid cells; N should be rounded up to a whole number);

A is the measured area (m^2).



HVAC QUALIFICATION OQ / PQ

Air flow velocity: fan type anemometers



It is a sensor to measure air speed in ducts or at ventilation grid.

The sensor may be connected directly with a computerized acquisition system



HVAC QUALIFICATION OQ / PQ



Measurement of air volume and uniformity – air exchange rate:

- this procedure / verification is used to determine average airflow volume and uniformity of volume within a clean room, clean zone or unidirectional flow work zone,
- the airflow volume is measured from each terminal filter or supply diffuser by using an electronic micro-anemometer with an appropriate airflow hood in a manner that includes all of the air issuing from each single source,
- the uniformity should not exceed 1%, unless otherwise specified,
- total air volume will, in turn, be used to determine the air exchange rate (room air volume per hour) for the clean room, as defined
  "air exchange rate = total airflow volume / volume of the room".

AHU-01

Room				Air outlet no.	air flow rate [CMH]		Air Change per Hour		Pass? [Yes/No]
Code	Name	Class	Volume [m^3]		Design value	Measured value	Acceptance Criteria	Measured value	
Total air flow rate [CMH]									
Total air flow rate [CMH]									
Total air flow rate [CMH]									
Total air flow rate [CMH]									
Total air flow rate [CMH]									
Total air flow rate [CMH]									
Total air flow rate [CMH]									

HVAC QUALIFICATION OQ / PQ



Air changes measurement: flow hood

Direct Inflow Measurement Hood

HVAC QUALIFICATION OQ / PQ



Determination of airflow patterns:

- to verify that the airflow pattern within work area is as designed (at rest) and to verify the interactions of airflow and equipment and the effectiveness of aerodynamic barriers (in operational),
- recommended where aerodynamic barriers are employed instead of physical barriers (A/B areas) and where therefore acceptable differential pressures cannot be achieved,
- also recommended for the initial qualification in "at rest" mode of clean room to show the absence of dead zones, backflows, leaks or turbulences which may contaminate a critical part of a clean area,
- consists in a visualisation of the air flow patterns, using for example Dräger smoke tubes (non toxic aerosol), or foggers
- to be accepted, such tests must be documented using video techniques.

HVAC QUALIFICATION OQ / PQ



Air flow visualisation testing (smoke test)







Drager smoke tube

HVAC QUALIFICATION OQ / PQ



Filter installation leak test (challenge test):

- to confirm that HEPA and ULPA filters are properly installed by verifying there is no by-pass leakage in the installation (frame, gasket seal and filter frame) and the filters are free of defects and small leaks,
- required for unidirectional airflows, but has only limited value for non-unidirectional airflow systems,
- performed by introducing an aerosol challenge upstream of the filters. Holding a particle counter probe at about 2.5 cm from the filter surface of the downstream side, scan the surface area and filter gasket frame,
- acceptable when no leak greater than 0.01% of upstream concentration is found: 100 (C_d / C_u)

C_d = downstream conc. of aerosol - C_u = upstream conc. of aerosol

LEAK TESTING FILTERS







HVAC QUALIFICATION OQ / PQ



DOP / PAO HEPA filter integrity

DOP = di-octyl phtalate
PAO = Poly Alpha Olefin (emery oil)
DEHP = di-(2-ethylhexyl)phtalate







B.7.2.5 Determination of scan rate

The probe traverse scan rate S_r should be approximately $15/W_p$ cm/s[18]. For example, when using a 3 cm × 3 cm square probe, S_r is 5 cm/s.

B.7.2.6 Procedure for installed filter system leakage scan test

The test is performed by introducing the specific challenge aerosol upstream of the filter(s) and searching for leaks by scanning the downstream side of the filter(s) and the grid or mounting frame system with the photometers probe as follows:

a) the airflow velocity test (B.2) for initial qualification should be done prior performing this test;

   NOTE Where installation is operated in a different airflow rate condition, the highest level should be selected for this test.

b) measurements of the aerosol upstream of the filters according to section B.7.2.3 should be taken first to verify the aerosol concentration and also its distribution homogeneity;

c) the probe should then be traversed at a scan rate not exceeding the value for S_r stated in B.7.2.5, using slightly overlapping strokes. The probe should be held in a distance of approximately 3 cm from the downstream filter face or the frame structure;

d) scanning should be performed over the entire downstream face of each filter, the perimeter of each filter, the seal between the filter frame and the grid structure, including its joints;

e) measurements of the aerosol upstream of the filters should be repeated at reasonable time intervals between and after scanning for leaks, to confirm the stability of the challenge aerosol concentration (see B.7.2.3).

B.7.2.3 Concentration of upstream aerosol challenge and its verification

The concentration of the aerosol challenge upstream of the filter should be between 10 mg/m³ and 100 mg/m³.

Appropriate measurements should be taken for the verification of the homogenous mixing of the added aerosol to the supply airflow. The first time a system is tested it should be determined that sufficient aerosol mixing is taking place. For such validation all injection and sampling points should be defined and recorded.

The upstream aerosol concentration measurements taken immediately upstream of the filters should not vary more than ±15 % in time about the average measured value. Concentrations lower than the average will reduce the sensitivity of the test to small leaks, while higher concentrations increase the sensitivity to small leaks. Further details as to how to conduct the air-aerosol mixing test should be agreed upon between customer and supplier.

HVAC QUALIFICATION OQ / PQ



Determination of room classification (airborne particle count):

- this test is performed to establish that a clean room meets the cleanliness class requirements (ISO class, GMP class),
- to identify the number and location of sampling points,
- to measure the concentration of particles of a well defined size (0,5 and 5 micron size),
- all sample points must comply with the particle class limit.

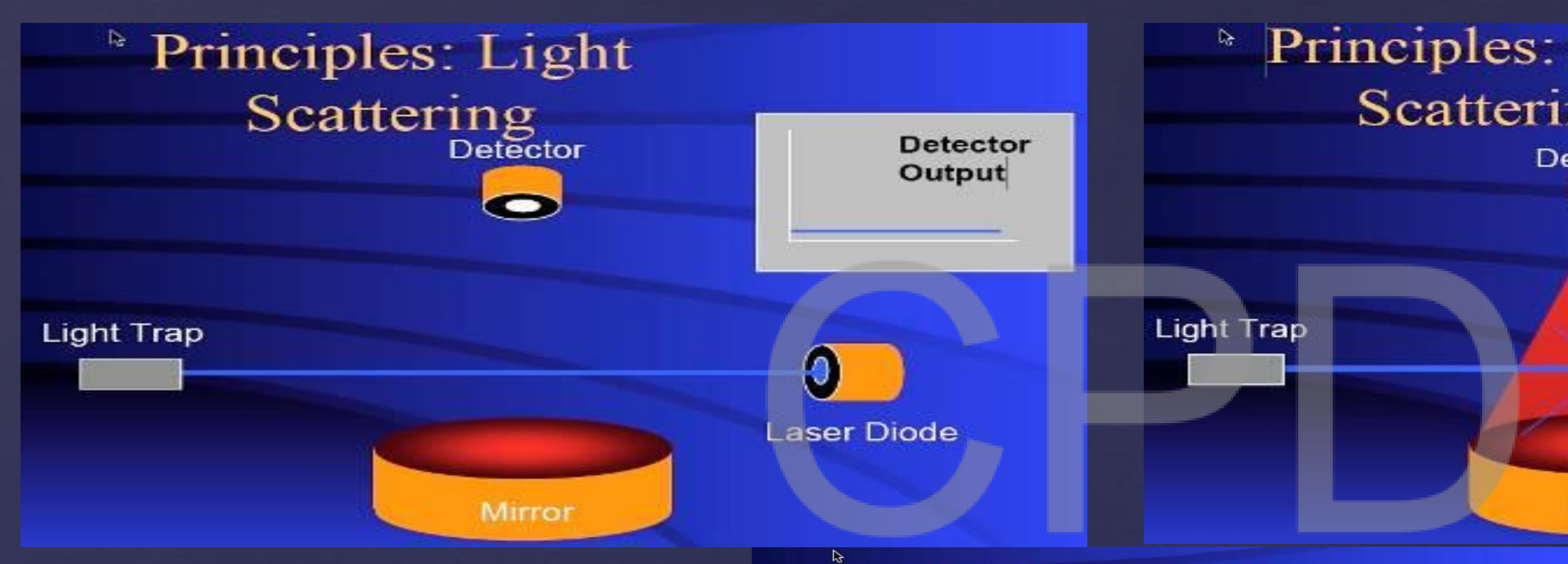
In case of A class, this test must be repeated in "operation conditions" to take into account generation of particles by operators, equipment or processes;

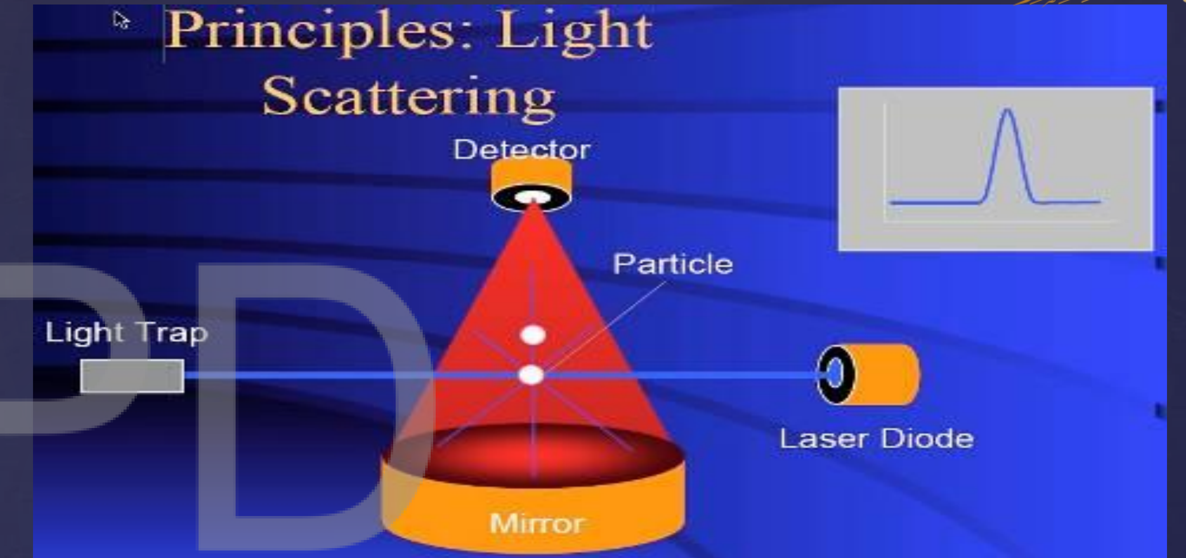
then the main purpose is to identify the worst case positions which should also be taken into account when installing probes for a continuous particle monitoring.

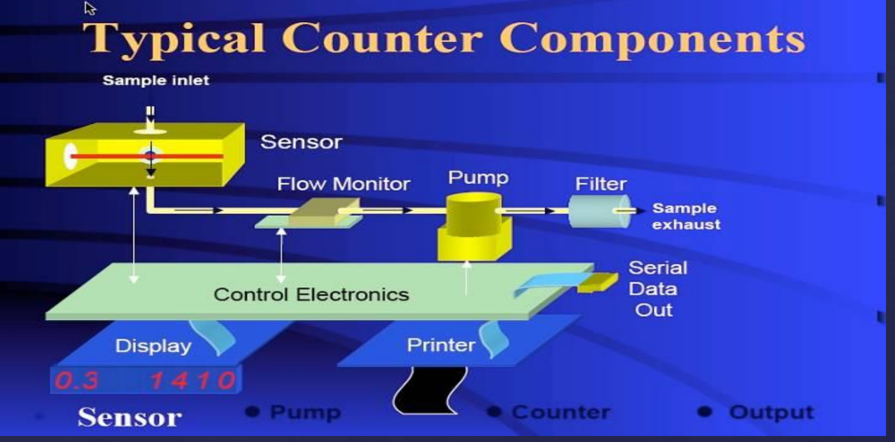
HVAC QUALIFICATION OQ / PQ



PARTICLE MONITORING







HVAC QUALIFICATION OQ / PQ



Determination of the recovery time:

- this test is performed to determine if a clean room or clean area is able to restore its specified cleanliness class within a predetermined time, after being exposed to a source of airborne particulate contamination (challenge) in form of smoke or aerosol,
- the result of this test provides important information for right operation of the HVAC system, because it defines also the minimum “hold“ time which should be taken into account after a power failure, contamination (i.e. hold time of changing rooms or pass box).

HVAC QUALIFICATION OQ / PQ



Temperature level and uniformity test:

- the purpose is to demonstrate that the clean room / HVAC system is able to maintain air temperature within the specified limits,
- the result of this test can also be used to support qualification of the location of fixed installed temperature monitoring probes.

Humidity level and uniformity test:

- the purpose is to demonstrate that the clean room / HVAC system equipped with dehumidification units is able to maintain air humidity levels within the specified limits,
- the result of this test can also be used to support qualification of the location of fixed installed humidity monitoring probes.



HVAC QUALIFICATION

CLEAN ROOM MONITORING PROGRAMME

HVAC QUALIFICATION
CLEAN ROOM MONITORING PROGRAMME



- Parameters to be monitored: (Definition of alert and action limits)

1) Cleanliness level (Particulate count / Microbial count). Number of points/locations for monitoring determined, specified, documented in procedure and protocol **(risk analysis)**;
2) Temperature and Rh% (Sufficient time for exposure and suitable sample size).
3) Differential pressure between areas.
4) Differential pressure across filters.
5) Air speed (In UDF/LAF).

HVAC QUALIFICATION
CLEAN ROOM MONITORING PROGRAMME



Mobile particle monitoring or discrete particle counter:

the particle counter is taken from one sampling point to another, according to a fixed sampling plan (SOP).

Only one sampler is needed to monitor sequentially the sampling points.





HVAC QUALIFICATION
CLEAN ROOM MONITORING PROGRAMME

Stationary on-line monitoring:
the particle counter is installed in a fixed position and is permanently connected to its sampling probe.
The sampling is continuous, without interruptions.
Every sampling point needs its own sampling probe/counter.
An automatic data transfer is needed.
The system requires low personnel.



HVAC QUALIFICATION
CLEAN ROOM MONITORING PROGRAMME



Is stationary or mobile particle monitoring recommended?
There is no fixed rule….the rationale comes from GMP guideline.

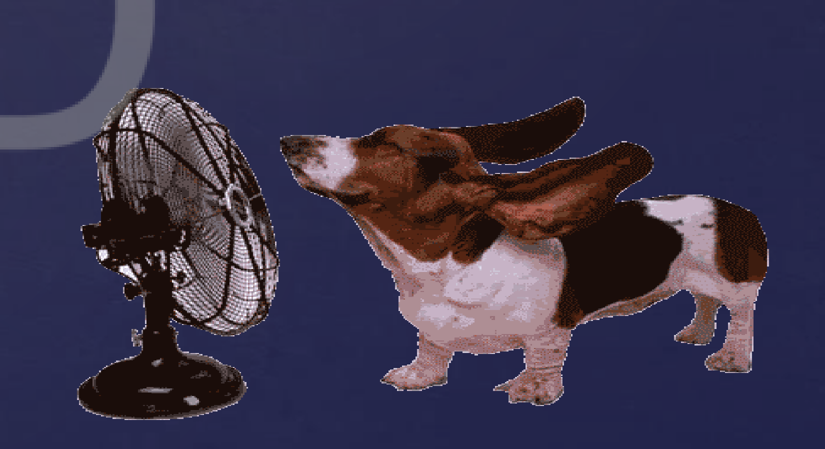
A areas:
stationary … because continuous measurements are required.

B areas:
… continuous measurements are recommended.

C/D areas:
mobile measurements are acceptable.



1. GMP manufacturing environments
2. HVAC systems
3. HVAC design requirements
4. HVAC qualification, risk assessment
5. Inspecting HVAC



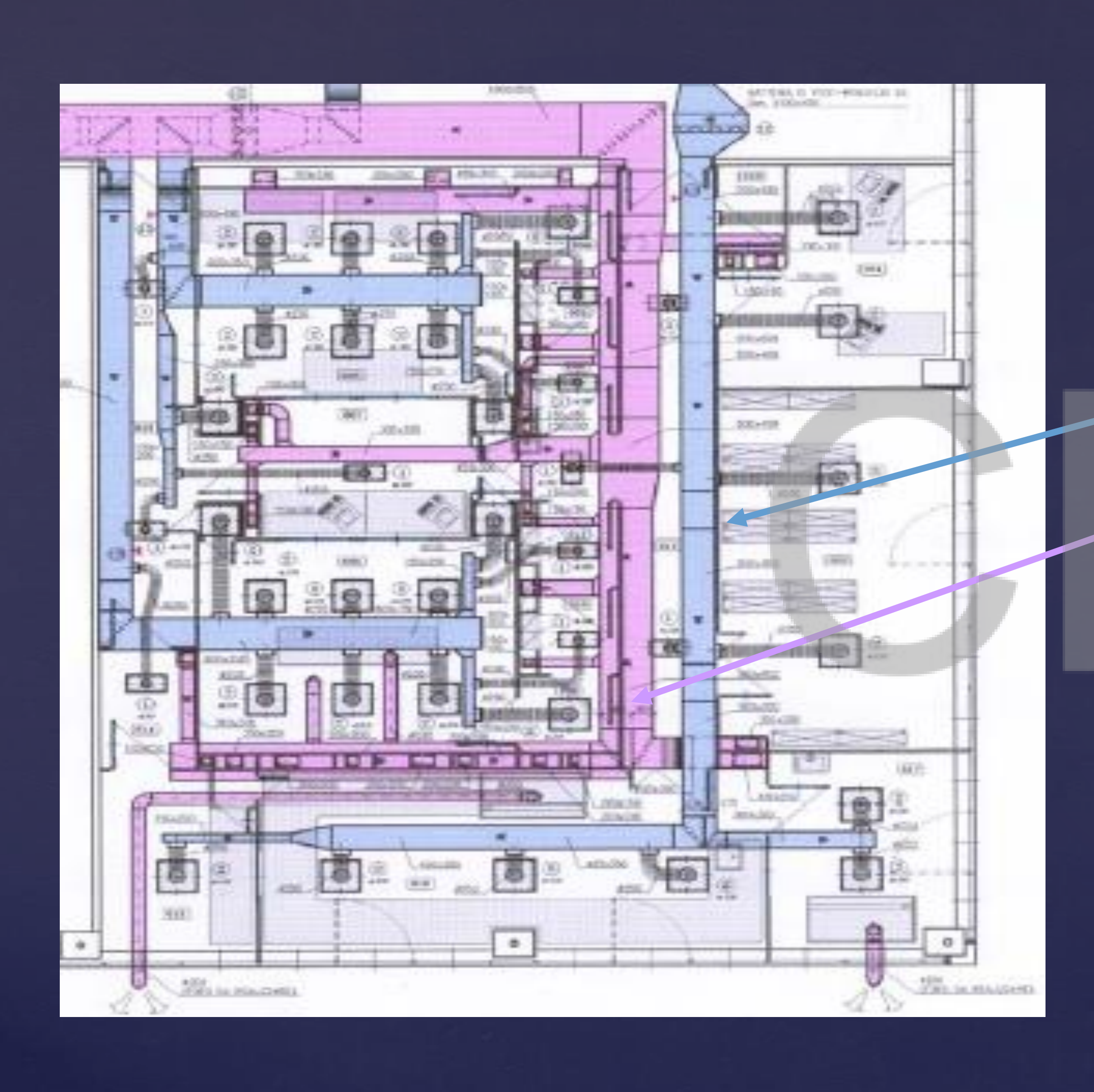
INSPECTING HVAC



- Verification of design documentation including description of installations and functions, requirements and specifications.
- Standard operating procedures.
- Maintenance / calibration program and records.
- Training files (program, records, evaluation).
- Environmental data, records and trend.
- Evaluation of OOS, OOT.
- Walking around the plant.

INSPECTING HVAC





Lay out:
air supply ducts
air return ducts

INSPECTING HVAC



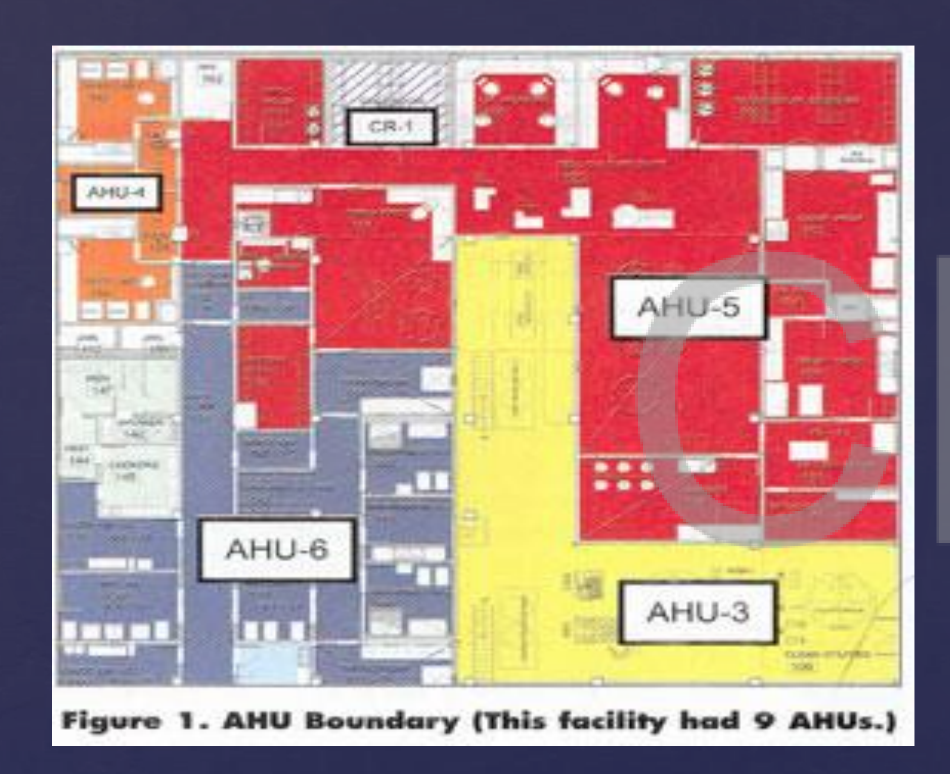


Figure 1. AHU Boundary (This facility had 9 AHUs.)

Layout:
Distribution of AHUs
(possibility of cross-contamination)

INSPECTING HVAC



ATM
ATM
CLASS 100 (AT REST)
CLASS 10,000
STERILE AHU
T/RH
FILLING
CHANGE ROOM -III
CHANGE ROOM -II
CORRIDOR
AIR LOCK
PREPARATION
WASHING AND STERILISATION
SEALING PACKING

Figure 4 : Typical airflow diagram for sterile area

P&ID HVAC system

INSPECTING HVAC



STAG & RAG WITH VCD
BYPASS
VCD
COIL
VCD
10 MICRON FILTER
VCD
HEATER BOX
M
M
FILTER PLENUM
FD
0.3 MICRON FILTER
3 MICRON FILTER
VCD
FRESH AIR
20 MICRON
10 MICRON
FD
SAG (TYP)
MODULATING DAMPER (TYP) PNEUMATICALLY OPERATED
EXHAUST
RAG (TYP)
WASHROOM
WASHROOM
OTHER PRODUCTION AREA
MILLING
FBD
RMG

Fig. 6.2: Air Conditioning Flow Diagram with Variable Air Volume System

P&ID
HVAC system

INSPECTING HVAC



13 1 2 3 4 5 6 7

12

10

11

8 8 8

HEPA filter (TYP)

Process space (TYP)

9 9 9

Low return (TYP)

LEGEND

1. 35% filters
2. 85% filters
3. preheat coil
4. cooling coil
5. fan section
6. humidifier
7. air monitoring device
8. constant volume reheat box
9. constant volume box
10. return fan
11. relief air damper
12. return air damper
13. outdoor air damper

INSPECTING HVAC



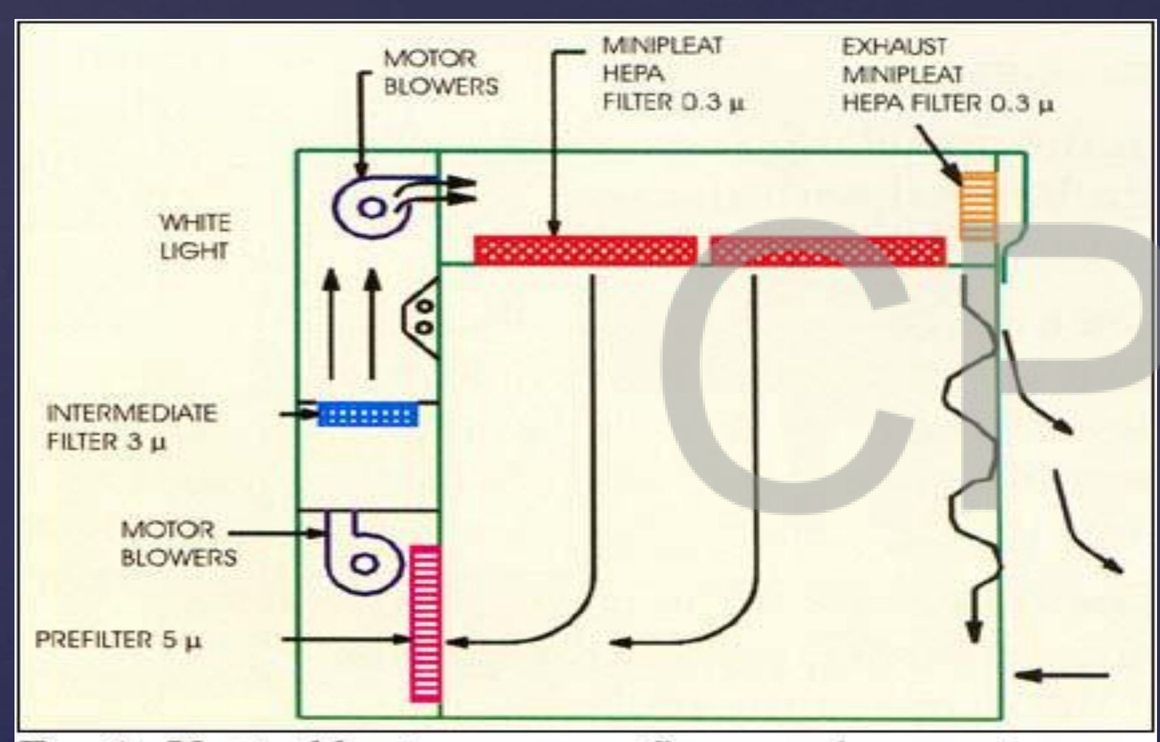


Fig. 4 : Vertical laminar reverse flow powder containment station

HVAC system: schematic drawing

INSPECTING HVAC



Gruppo: Filtri grado HEPA (H)
Classe: H 12 EN 1822
Efficienza:
- globale E ≥ 99,5% MPPS
- a 0,3 µm Ei ≥ 99,99% EU13
Collaudo: individuale su 100% dei filtri
Media: Carta in fibra di vetro

HEPA grade

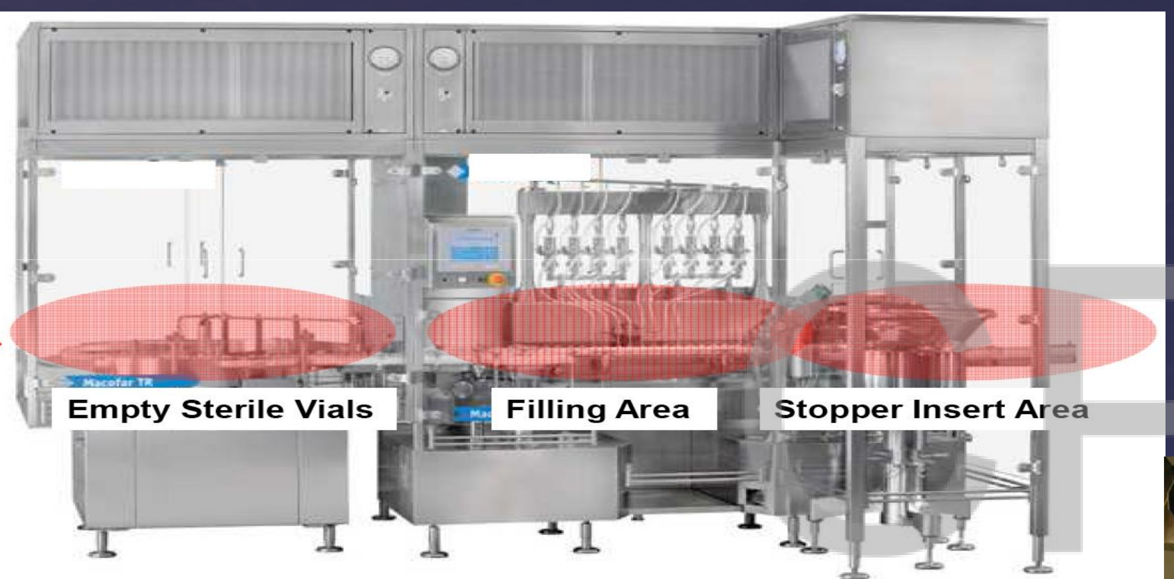
Class H12

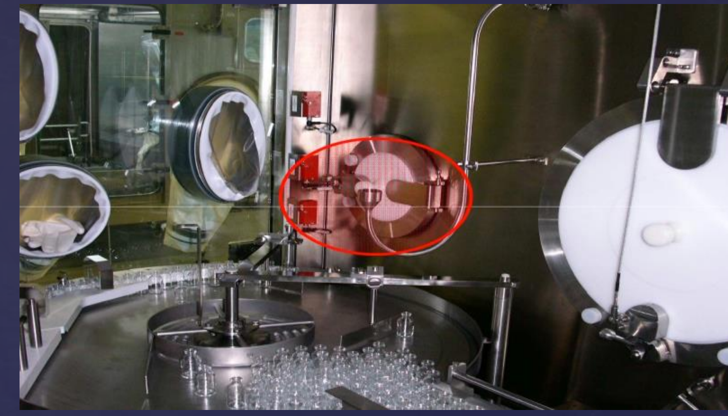
Filter certificate

5

INSPECTING HVAC









Particle counter



RISK ASSESSMENT

To explain the concept of a risk based approach in more details, the "grade C clean rooms" are presented as example.
The system “grade C clean rooms” consist of the subsystems which are GMP-relevant because it has an indirect influence on the product quality as per following:

- Clean room hardware (walls, floor, ceiling, etc.)
- HVAC system
- HVAC control system (e.g. BMS)

Critical process parameters for the grade C clean rooms are

- Temperature
- Room pressure
- Relative humidity
- Air exchange rate (supplied air volume)
- Particle concentration in the air
- Microbial contamination
- Cleaning properties



RISK ASSESSMENT

The following control measures are planned to control and monitor the critical process parameters of the clean rooms (and to maintain the qualified state later on):

- GMP monitoring system: A qualified data recording system will continuously (online) monitor the room pressure, temperature and relative humidity in the clean rooms. Alarms will be triggered and documented if limits set for critical parameters are exceeded or under-run.
- Regular offline monitoring: The particle concentration and microbial contamination is monitored offline at regular intervals to assure compliance with the requirements defined in the regulations.
- Regular requalification: Classification of the clean rooms, determination of the air exchange rate and integrity testing of the HEPA filters is performed at regular intervals to keep the clean rooms in a qualified state.
- Regular maintenance / calibration: Maintenance and / or calibration of relevant components are performed at regular intervals to maintain the qualified state.

RISK ASSESSMENT



No.	Component	Functions	Failure	Cause	Impact	Risk Type	Control Measures	S	Comment	P	Comment	D	Comment	RPN	Criticality	Remarks	Implementation in
1	Room surfaces (floor, walls, doors, ceiling, windows, etc.)	Physical boundaries to other rooms and parts of the facility	Defects (cracks, gaps, holes, etc.)	Material defect, bad construction	Bad cleaning / decontamination properties	GMP	None	2	Potential impact on critical process parameters	2	Occasional mistakes during the construction are likely	3	No control measures planned so far	12	high		Technical design (DQ), IQ, OQ
2	Room conditions (temperature, humidity, pressure), observed by the GMP monitoring system	Reproducible conditions for processing	Deviation of conditions in the room from the acceptable range	Sensors of the GMP monitoring system have not been adequately positioned / conditions are not homogen throughout the room	Irreproducible conditions for processing	GMP	None	2	Potential impact on critical process parameters	3	Inhomo-geneous conditions are likely	3	No control measures planned so far	18	high	Sensors for the measurement of room conditions and alarms are within the scope of the GMP monitoring system	Functional design (DQ), IQ, OQ
3	Room conditions (air exchange rate, particle concentration, microbial contamination), NOT observed by the GMP monitoring system	Reproducible conditions for processing	Deviation of conditions in the room from the acceptable range	Malfunction of the control system, defect terminal HEPA filters, inadequate handling of the rooms	Irreproducible conditions for processing, potential source of contamination	GMP	None	2	Potential impact on critical process parameters	2	Occasional defects / handling errors may occur	3	No control measures planned so far	12	high	Qualification includes regular requalification and off-line monitoring of these parameters to maintain the qualified state	Functional design (DQ), IQ, OQ
4	Monoblock	Housing of the fans, heat exchangers, etc.	Defects (leaks, etc.)	Material defect, bad construction	Deviation from the acceptable room pressure, air exchange rate	GMP	GMP monitoring system, regular maintenance / room requalification	2	Potential impact on critical process parameters	2	Occasional mistakes during the construction are likely	1	See safeguards	4	low		
5	Fans (supply / exhaust air) incl. frequency converter and motor	Driving of the air flow	Malfunction	Defect, wear	Deviation from the acceptable room pressure, air exchange rate	GMP	GMP monitoring system, regular maintenance / room requalification	2	Potential impact on critical process parameters	1	Regular maintenance	1	GMP monitoring system / regular requalification	2	low		
6	Air dehumidifier	Air drying	Malfunction	Defect, wear	Deviation from the acceptable humidity	GMP	GMP monitoring system, regular maintenance	2	Potential impact on critical process parameters	1	Regular maintenance	1	GMP monitoring system	2	low		
7	Air humidifier	Air humidification	Malfunction	Defect, wear	Deviation from the acceptable humidity	GMP	GMP monitoring system, regular maintenance	2	Potential impact on critical process parameters	1	Regular maintenance	1	GMP monitoring system	2	low		

RISK ASSESSMENT

The Risk Assessment will define whether or not the component is sufficiently controlled by the control measures:

- Components which have an influence on the **temperature, relative humidity and / or the room pressure** will be independently monitored by the GMP monitoring system. Parameter values exceeding or under running defined limits due to a malfunction of a component will lead to an alarm.
- Components which have an influence on the **air exchange rate** (supplied air volume) are covered by the GMP monitoring system because significant changes in the supplied air volume will likely lead to a deviation of the room pressure. Furthermore, the air exchange rate is subjected to the regular requalification.
- Components influencing the **particle concentration** and the **microbial contamination** (HEPA filters) are covered by the control measures listed above, but an online monitoring (and therefore an immediate, independent control) is not possible. Furthermore, the particle concentration and the microbial contamination are very critical parameters in a clean room. Thus, HEPA filters are subjected to the qualification and regular requalification.
- d) Components influencing the **cleaning properties** are not covered by control measures, remain therefore GMP-relevant and are subjected to the qualification and maintenance, if need be.



REFERENCES

- FDA Guidance for Industry – Sterile Drug Products produced by Aseptic Processing (Sept. 2004)
- USP NN – General Information <1116> Microbiological evaluation of clean rooms and other controlled environments
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- ISO 14644 Part (1-7): clean rooms and associated controlled environments
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- WHO training modules

REFERENCES



This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization

WHO Technical Report Series

961

CPD

WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Annex 5

Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms


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CPD



CPD

Thank you


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CPD
CENTER FOR CONTINUING
PROFESSIONAL DEVELOPMENT
مركز التطوير المهني المستمر

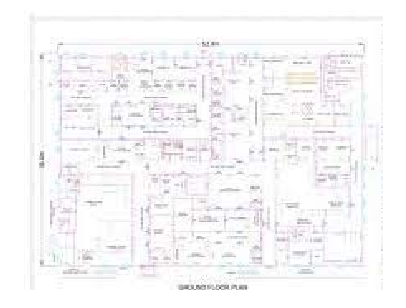


Pharmaceutical plant design

(Lecture 1)



PRESENTED BY: Amal Adel



Content

1. Introduction
2. Accomodatiom schedule
3. Lay out
4. contruction

Content

1. Room Cleanliness
2. Material &Personnel flow
3. Room Data Sheet
4. classification

3

Content

1. pressure difference
2. Warehouses
3. Oral solid dosage form
4. Liquid and semi solid dosage form

1-Introduction



- Layout of building and services

Means all *buildings* where *manufacture* of the products will take place.

Conditions that's exist within them and the area of location.

Introduction



-Important to understand the manufacturing processes and conduct the facility programming.

-Facility layout must be an integrated design that satisfies the following:

- Process requirements
- Personnel flows
- Material flows (product, component (including packaging materials and raw material movements)
- Equipment layout requirements
- Operational access requirements
- *Maintenance* access requirements



-The firm must define their true needs…they must separate the "must have" objectives from their "wants" objectives.

This is often a very time consuming effort, since each department needs to re-think what is truly mandatory for their operation versus those items that are desirable, but not essential to successful operations.

Formal decision analysis may need to be performed



-The designer must first understand the product and process requirements.

Accommodation Schedule is the first step Accommodation conceptual equipment and schedule layout facility layout



Accommodation Schedule



Accommodation Schedule:

- Defines all areas that can influence unit operations required for manufacturing as well as the relationships and flows between them
- Materials and personnel are primary focus
- Can be developed once the process is known – All process flow diagrams should be complete
- Also referred to as logic diagrams, or bubble diagrams

Accommodation Schedule



EXTERNAL AREA

Factory Change

CORRIDOR

Personnel - Clean Change

Equipment Airlock

Preparation Area

Aseptic Change/ Gown

AUTOCLAVE

ASEPTIC CORE

INSPECTION & SECONDARY PACKAGING

Accommodation Schedule

Conceptual Layout



Conceptual Layout

- Derived from Accommodation Schedule and equipment sizing needs
- Building *blocks of equipment lines* are developed
- *Blocks of rooms* are assembled based on necessary process requirement.

Layout Design



Equipment Layout

- Scaled drawing derived from conceptual layout
- Defines *precise* room sizes, structural grids and access routes
- Building and fire codes are established in this phase. Building *blocks of equipment* lines are developed
- Blocks of rooms are assembled based on necessary adjacencies and process requirements
- Part of detail design phase of project life cycle

Layout Design



After Equipment Layout Drawings are prepared, establish Material and Personnel Flows drawings with directional *arrows*

- Primary purpose is to illustrate how to eliminate or minimize the potential for **contamination** of the clean room product and personnel.

- One-way flow always preferred

- Provide separate entry and exit ways of possible, particularly in changing areas.

Layout Design



Considerations

- Provide sufficient space for operations
- Provide sufficient space for movement, equipment access and egress for life safety code requirements
- Rooms must be sized *only after fully understanding what goes into the room*, and the process that takes place between the four walls
- Can’t overlook need for extra space *for portable items brought into the room*, such as carts.
- *Mechanical and electrical equipment panels* also need to be taken into account

Layout Design



<u>Cost considerations in layout design</u>:

- Layout has significant impact on the amount of materials and therefore facility cost
- Simple plan shapes are most economical – Square maximizes internal area,
- Minimize size of clean corridors and staging areas
- Minimize height of building to extent possible. Height increases cost due to:

– Increase in amount of perimeter wall for a given total floor area

– Increased load on the structure (Heavier load on columns and footings)

– Additional hoisting of materials and extra time taken by operators to reach the higher floors

Layout Design



Detailed diagrams depicting pressure cascades, air flow directions and flow routes for personnel and materials should be prepared and maintained

Layout Design



Personnel flows considered:

–Manufacturing personnel

–Maintenance personnel

–Quality control personnel

Material flows considered:

– Raw materials

– Finished goods

– Waste

– Product (In-process, Intermediate & Final)

-- Disinfectant

– Equipment • Clean and dirty components • Portable equipment and Product containers

Layout Design



- Adequate space for future extension.

– Availability of water supply (Quality and Quantity).

-





Principle

The layout and design should aim to:

- minimize risks of error
- Permit effective maintenance
- Avoid cross-contamination, build-up of dirt and dust
- Avoid any adverse effect on the quality of products.

Design……….

Process flow → Ensure logical flow
Material flow → Ensure logical flow
People flow → Ensure logical flow

Layouts



- **General layout**
- **AHU schematic diagrams**
- **Material flow (and personnel flow)**
- **Classification layout**
- **Differential pressure layout.**

Lay Out



- Floor no. , Type of activity, approval
- Clarification for hatches, emergency doors,
- Pass boxes (type and class)
- Abbreviations and color coding (distinguishable colors)
- Unified Traceable coding system for rooms, airlocks and pass boxes (HVAC qualification, AHU diagrams, Layouts..)
- Size & resolution

Construction



1-Suitable materials

2-Electrical supply

3–Suitable lighting

4-Temperature and relative humidity control

5- Appropriate and effective ventilation

These may affect products during manufacture or storage as well as functioning of equipment.

1-Suitable materials



Production areas finishing

-General: smooth, monolithic, cleanable, chip resistant with minimum seams, joints and no crevices or molding

-Floors: kota, sheet vinyl, epoxy or polyester coating with carried up walls base or raised floor with and without perforations using the above materials

-Walls: Plastic, epoxy or polyester coating with carried up wall base or raised floor with and without perforations using the above materials

-Ceilings: Enamel, plaster covered with plastic, epoxy or polyester coating or with plastic-finished acoustical tiles when entire ceiling is not fully HEPA filtered.

Production Area



Doors should be carefully designed to avoid uncleanable recesses; sliding doors may be undesirable for this reason.

2- Electrical Supply



Electricity

Continuity of electrical supply is essential for a number of systems or processes (air supply and extraction, particularly for sterile manufacture; incubators; stability chambers) and thus backup systems should be available in the event of mains failure.

3- Lighting



Suitable lighting

-Lighting levels should be adequate to permit operators to do their work properly, accurately and attentively.

-Lighting of production and packing areas should be enable good vision.



3-Lighting



Suitable lighting level requirements

Illumination intensity (in Lux)	Specific Area
20	- narrow corridor, side
50	- warehouse for big size containers, corridor for personal traffic
100	- corridor for traffic of personnel and forklift, break room, locker rooms, rest rooms, utility rooms, staircase lobby
200	- workshop, warehouse
300	- laboratory
500	- offices with reading activities, production room, first aid room
750	- draft room
1000	- visual inspection
1 foot candle (ft c)= 1 lumen/ feet² (lm/ft²)= 10.764 lux	
Ref.: ASEAN Operational Manual for Implementation of GMP- 2000	

3- Lighting



Suitable lightening can be assumed from the following equation

$$N = \frac{\varphi * 1.25 * A}{\eta * \text{Lumens per lamp}}$$

Where, N= number of lights

φ = required lux

1.25 = maintenance factor

A = Room area in sq. mt.

η = coefficient of utilization ≈ 0.7

3- Lighting



- **Example:**

Required lux 300

Room size = 4m * 3m = 12 sq. mt

Tube light of 1*40 w gives 2700 lumen at working height

$$N = \frac{300 * 1.25 * 12}{\eta * 2700}$$

$= 2.38 \approx 3$ lights

3- Lighting



To avoid photo degradation, a suitable light using sodium vapor lamp is to be provided with dispensing/sampling booth for weighing/sampling of highly light sensitive materials.



4-Enviromental Monitoring



Temperature and relative humidity should be controlled, monitored and recorded, where relevant, to ensure compliance with requirements pertinent to the materials and products and provide a comfortable environment for the operator where necessary.

Maximum and minimum room temperatures and relative humidity should be appropriate. *Alert and action limits* on temperatures and humidities should be set, as appropriate.

4-Enviromental Monitoring



Cubicles, or suites, in which products requiring low relative humidity are processed, should have well-sealed walls and ceilings and should also be separated from adjacent areas with higher relative humidity by means of *suitable airlocks*.





- Different AHU serving different room
- air filtration
- air change rate or flushing rate
- room pressure
- location of air terminals and directional airflow

5- Appropriate and effective ventilation



Typically, in a room operating with turbulent airflow, the air should be introduced from ceiling diffusers, located at the door entry side of the room and extracted from the rear of the room at low level to help give a flushing effect in the room. Correct flushing of the rooms may be verified by airflow visualization smoke tests.

5- Appropriate and effective ventilation



Ventilation dampers, filters and other services should be designed and positioned so that they are accessible from *outside* the manufacturing areas (service voids or service corridors) for maintenance purposes.

5- Appropriate and effective ventilation





- Exhaust air discharge points on pharmaceutical equipment and facilities, such as from fluid bed driers and tablet-coating equipment, and exhaust air from dust extraction systems, carry heavy dust loads and should be provided with adequate filtration to prevent contamination of the ambient air.

- Where the powders are not highly potent, final filters on a dust exhaust system should be fine dust filters with a filter classification of F9 according to EN 779 filter standards.



5- Appropriate and effective ventilation



- Wherever possible, dust or vapour contamination should be removed at source. Point-of-use extraction, i.e. as close as possible to the point where
- the dust is generated, should be employed. Spot ventilation or capture hoods may be used as appropriate



Room cleanliness factor.



- material flow
- personnel flow
- gowning procedures
- equipment movement
- process being carried out (open or closed system)
- type of product
- cleaning standard operating procedures (SOPs).

Material &Personnel flow



- should be designed to provide easy movement of materials yet prevent product mix-ups, cross-contamination and contamination from the environment.

- Controls should prevent flow between areas with open containers and prevent unprotected personnel from entering areas where they could be exposed. (a path)

- Appropriate protective equipment should also be provided in the areas where personnel could be exposed to the material or product.

- flow (piping? Movable tank?) - **Waste flow**

Material &Personnel flow



- Personnel Flows

-Adequate room for personnel access for routine and non-routine maintenance.

-Personnel flows should be designed to:

-prevent contamination to products and materials

-ensure personnel safety..

-Personnel flow diagrams should be generated and used to facilitate the evaluation of the potential impact of personnel flows on API processes as well as raw materials and API products..



Material and Personnel flow



PRIMARY PACK. MAT. FLOW

SECONDARY PACK. MAT. FLOW

RAW MATERIALS FLOW

FINISHED GOODS FLOW

INTERMEDIATE MAT. FLOW

WASTE FLOW



Material and Personnel flow





Room data sheet



- Includes Temp. ,RH, Δ P & No. of air change to the class & the type of process.

→Room Pressure Differential (DP)
Cleanroom positive pressurization is desired to prevent infiltration of air from adjacent areas.

→Room Temperature (T)
Generally (20 ± 2 for clean area)

→%Relative Humidity (%RH)
Relative humidity (RH) may be 45% ± 5% or according to the product requirement
Effervescent powder or granules, soft gelatin capsule , ODF→ ↓ %RH

Room data sheet



- Number of Air Change (ACH/h)

$$= \frac{\text{Total Air Flow (m3/h)}}{\text{Room Volume (m3)}} = \quad / h$$

Room Name	Room Code No.	Temp.	RH.	Room Class	Room pressure	Total air flow	Room volume	No of air change ACH/h

Zoning (classification) layout





Pressure difference



Manufacturing facilities should normally be maintained at a positive pressure relative to the outside, to limit the ingress of contaminants. Where facilities are to be maintained at negative pressures relative to the ambient pressure, special precautions should be taken.

Pressure Difference



- Areas of same classes 5-20 pa (10).

Between the different classes 10-15 pa (15).

Doors opened towards more pressurized side



Pressure Difference



The pressure differential should be of sufficient magnitude to ensure containment and prevention of flow reversal, but should not be so high as to create turbulence problems.

Pressure Difference



The location of the negative pressure facility should be carefully considered with reference to the areas surrounding it, particular attention being given to ensuring that the building structure is well sealed.

Pressure Difference



Negative pressure zones should, as far as possible, be encapsulated by surrounding areas with clean air supplies, so that only clean air can infiltrate into the controlled zone.

Pressure Difference



Where different products are manufactured at the same time, in different areas or cubicles, in a multiproduct OSD manufacturing site, measures should be taken to ensure that dust cannot move from one cubicle to another.

Pressure Difference



Correct directional air movement and a pressure cascade system can assist in preventing cross-contamination. The pressure cascade should be such that the direction of airflow is from the clean corridor into the cubicles, resulting in dust containment.



Pressure Difference



The corridor should be maintained at a higher pressure than the cubicles, and the cubicles at a higher pressure than atmospheric pressure.

Pressure Difference



- -The pressure cascade regime and the direction of airflow should be appropriate to the product and processing method used.
- The pressure cascade for each facility should be individually assessed according to the product handled and level of protection required.
- ex Highly potent products should be manufactured under a pressure cascade regime that is negative relative to atmospheric pressure



General considerations



When dealing with particularly harmful products, additional steps, such as handling the products in glove boxes or using barrier isolator technology, should be used.

Pressure Difference



- - Building structure should be given special attention to accommodate the pressure cascade design.air lock
- -Ceilings and walls, close fitting doors and sealed light fittings should be in place, to limit ingress or egress of air.

Pressure Difference



- Doors should open to the high pressure side, so that room pressure assists in holding the door closed and in addition be provided with self-closures.

- Should the doors open to the low pressure side, the door closure springs should be sufficient to hold the door closed and prevent the pressure differential from pushing the door open.

Pressure Difference



- There should be a method to indicate if both doors to airlocks are open at the same time, or alternatively

- These should be interlocked, The determination of which doors should be interlocked should be the subject of a risk assessment study.

Pressure Difference



- Adequate room pressure differential indication should be provided so that each critical room pressure can be traced back to ambient pressure

- Room pressure indication gauges should have a range and graduation scale which enables the reading to an accuracy, as appropriate; normal operating range, alert and action limits should be defined and displayed at the point of indication.

- A colour coding gauge may be helpful.

Pressure Difference



The pressure control and monitoring devices used should be calibrated and qualified. Compliance with specifications should be regularly verified and the results recorded. Pressure control devices should be linked to an alarm system set according to the levels determined by a risk analysis.





Pressure Difference Question



- Review the differential pressure
- Which room is applicable?



Differential pressure



Room 1
30 Pa
D

Room 2
60 Pa
A
LF
Air Lock
45 Pa
B

Room 3
45 Pa
Air Lock
C

30 Pa
D
Passage
15 Pa
Air Lock
0 Pa

Air Lock

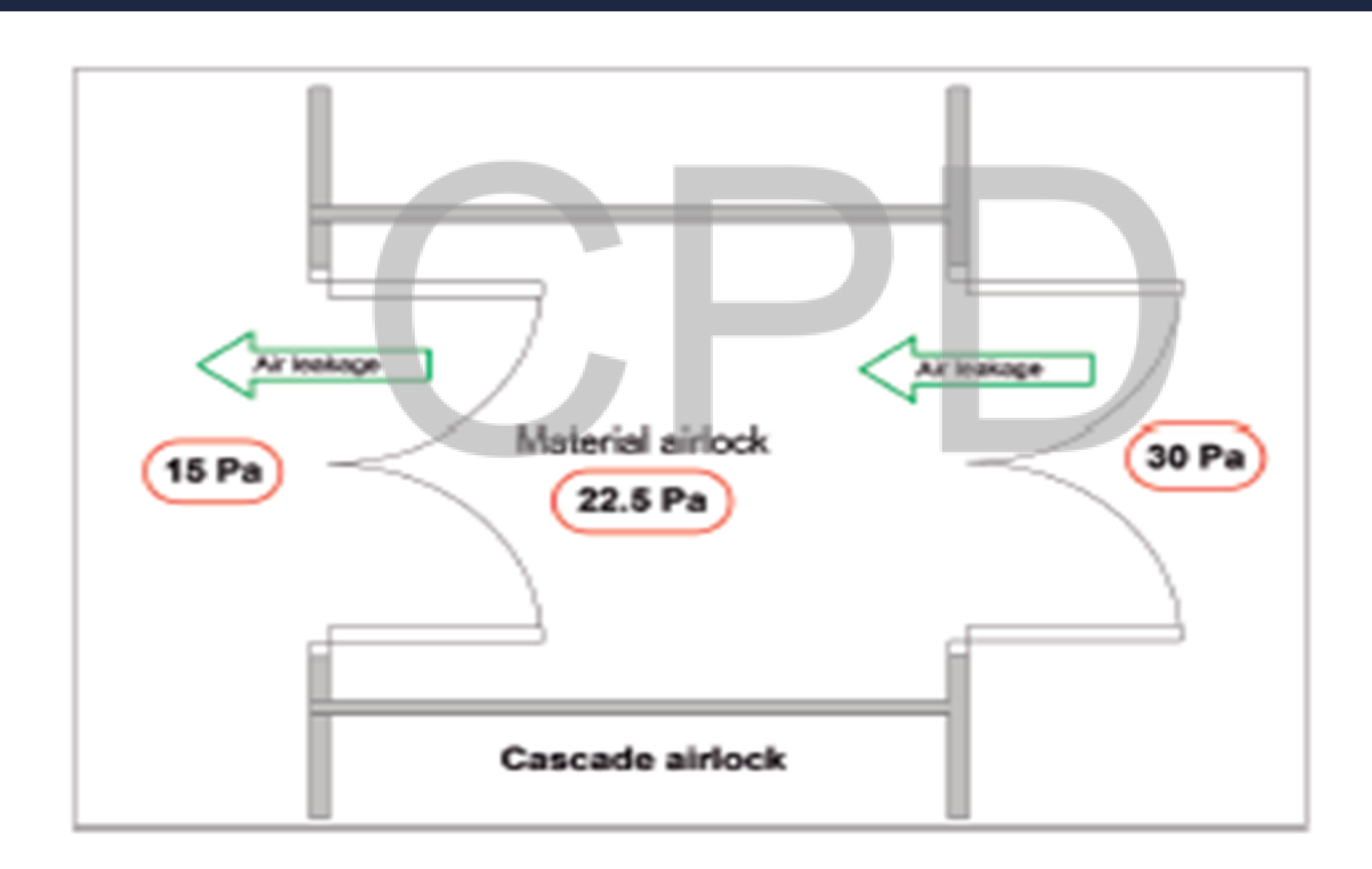


Airlocks with different pressure cascade regimes include the cascade airlock, sink airlock and bubble airlock:

- cascade airlock: higher pressure on one side of the airlock and lower pressure on the other;
- sink airlock: lower pressure inside the airlock and higher pressure on both outer sides;
- bubble airlock: higher pressure inside the airlock and lower pressure on both outer sides.

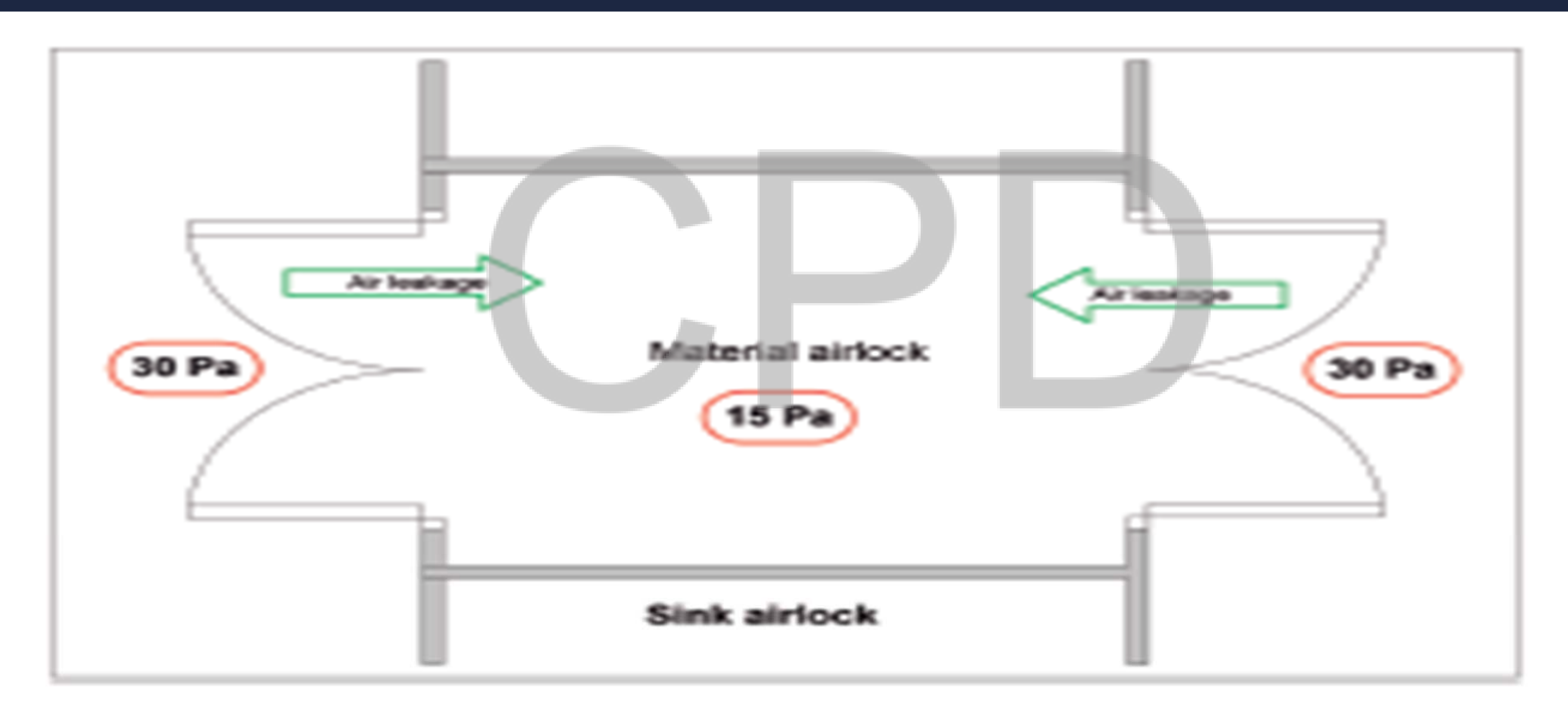
Air locks

A- Cascade



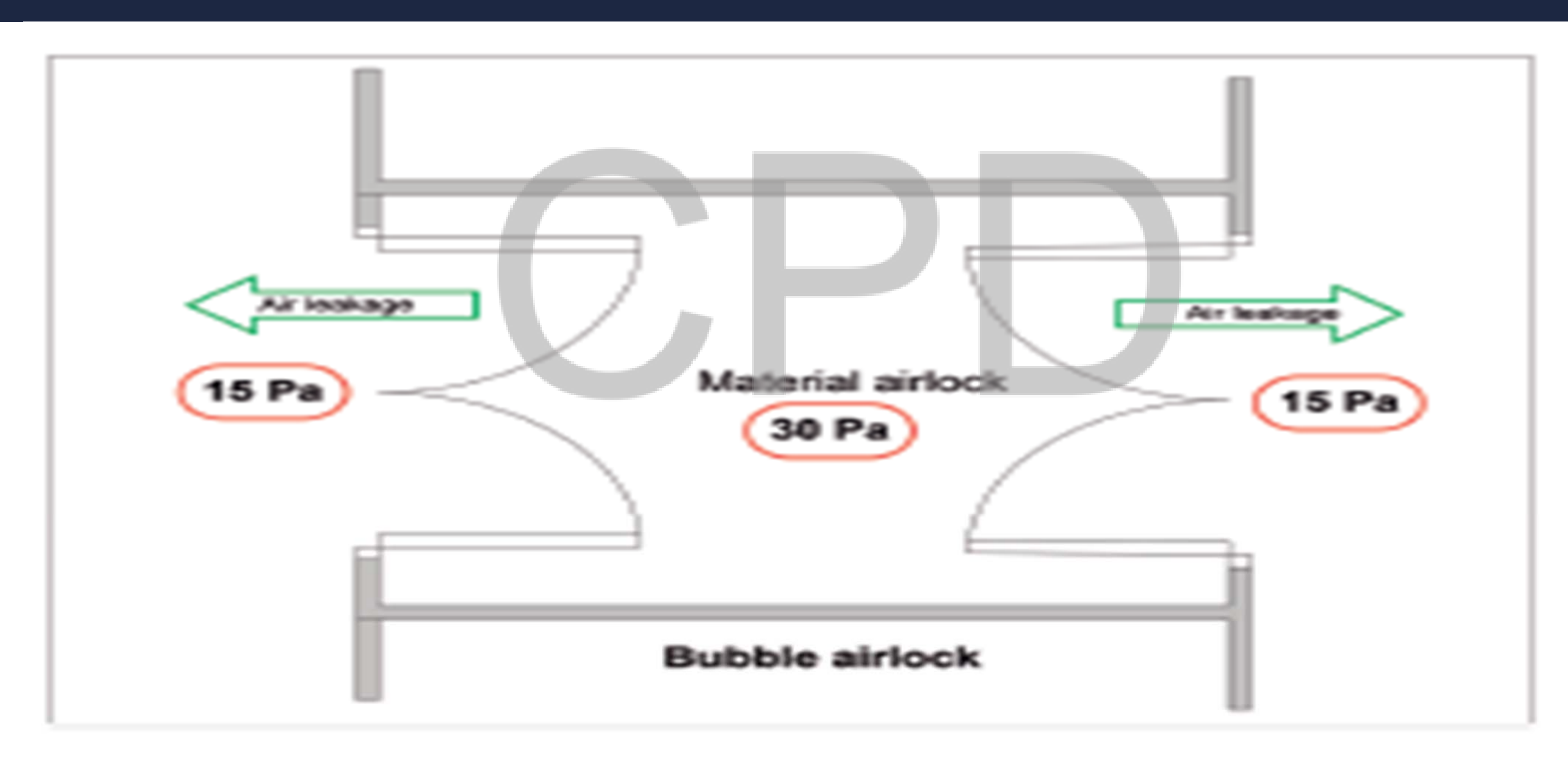
Air locks

B-Sink



Air Lock

C- Bubble



Airlocks

MAL & PAL.....



- adequate airlocks, such as personnel airlocks (PAL) and/or material airlocks (MAL), change rooms and passages should be provided to protect passage between different cleanliness conditions . *These should have supply and extract air systems as appropriate.* should be designed so that the required pressure cascades can be achieved;

- The final stage of the changing room should, in the "at rest" state, be the same GMP classification grade as the area into which it leads.

Air locks

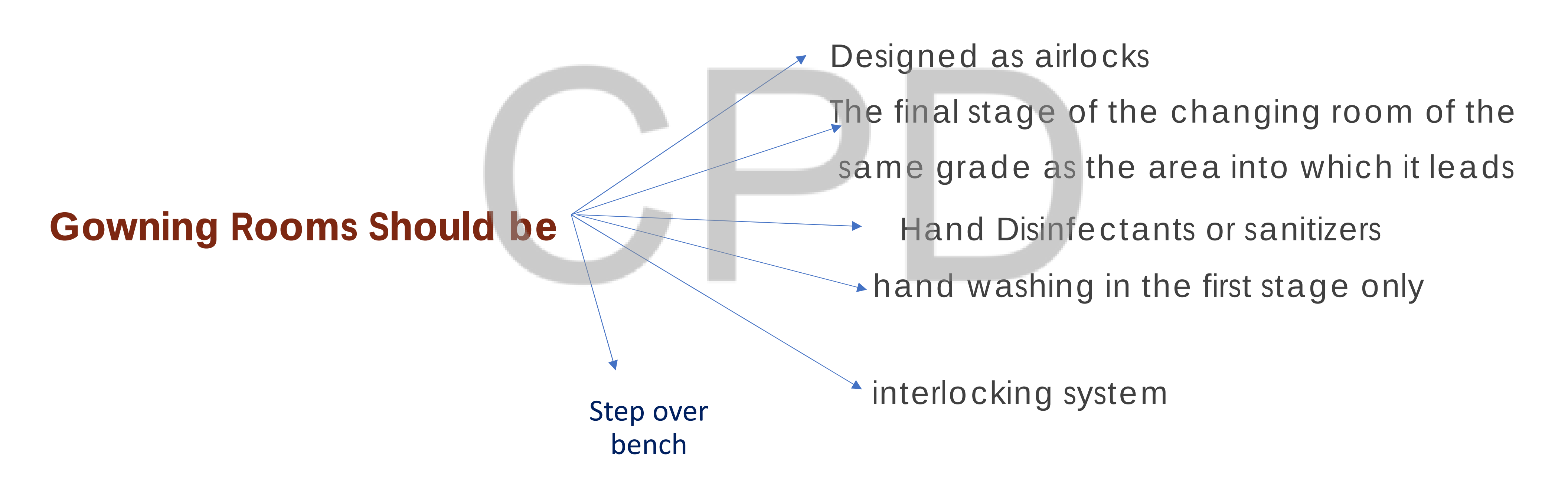
MAL & PAL



Personnel and materials should not move from a higher cleanliness zone to a lower cleanliness zone and back to a higher cleanliness zone; (if moving from a lower cleanliness zone to a higher cleanliness zone, changing /decontamination procedures should be followed)

Air locks

PAL



PAL



Mirror

Illustration

Air Locks

Interlocking system



Airlock doors should not be opened simultaneously. An interlocking system and a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.

Air locks

MAL & PAL



PTH &PB



Material pass-through-hatches (PTH) or pass boxes (PB) can also be used for separating two different zones. PTHs fall into two categories, namely a dynamic PTH or a passive PTH. Dynamic PTHs have an air supply to or extraction from them, and can then be used as bubble, sink or cascade PTHs.

Rest Area



Rest and refreshment rooms should be separated from manufacturing and QC areas.



QC



- QC laboratories should be separate from production areas
- Separate areas for biological, microbiological and radioisotope methods
- Suitable design with sufficient space to avoid mix-ups and cross-contamination
- Suitable space for storage, samples, reference standards, solvents, reagents and records • Prevention of fumes • Separate air supply • Well designed ventillation



Warehouses



Warehouses



-There should be sufficient space, lighting and ventilation to ensure required segregation, appropriate storage conditions and cleanliness

-Appropriate controls and segregation should be provided for products requiring specific handling or storage conditions, such as products containing hazardous substances and products to be stored under controlled temperature and relative humidity conditions. (cool store, cold store)

Warehouses



- Storage areas of sufficient capacity
- Separate and segregated areas: starting materials, packaging materials, intermediates, bulk, finished products, quarantined, released, rejected, returned and recalled products and materials
- Appropriate temperature and relative humidity conditions within defined limits • Provided, controlled, monitored and recorded
- Storage conditions in label
- Normal conditions: 15-30 ˚C
- Cool room: 8-15 ˚C
- Cold: 2-8 ˚C
- Protect from humidity: less than 60%

Warehouses



Storage areas

Quarantine area: clearly marked and access restricted

A separate sampling area is the norm: no risk for contamination or cross-contamination (sampling booth)

Segregated areas for rejected, recalled and returned materials and products

Safe and secured areas for narcotics and other materials (risk of abuse, fire, explosion, hazard)

Special attention to safe and secure storage for printed packaging material

Warehouses



-receiving and dispatch bays should be separate, to avoid mix-ups.

- Bays should protect products from weather conditions.

-Checking transport conditions (SOP , checklist)

-Premises should be protected from the entry of birds, rodents, insects and other animals.(air curtains- double door interlocked)

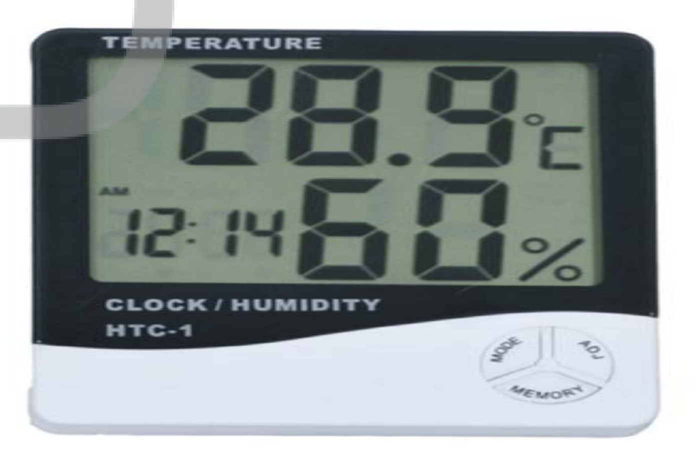
-Following sampling, the goods should be subject to quarantine. Batch segregation should be maintained during quarantine and all subsequent storage.

Warehouses



Mapping studies for temperature, and relative humidity where appropriate,

should be done, for example in storage areas, cool &cold area



Warehouses



Measures should be taken to ensure that rejected medical products cannot be used. They should be segregated and securely stored while awaiting destruction or return to the supplier. (flow to outside)

Warehouses



Narcotic medical products should be stored in compliance with international conventions, national laws and regulations on narcotics

Warehouses



Combustible liquids and solids and pressurized gases, should be stored in a dedicated area that is subject to appropriate additional safety and security measures, and in accordance with national legislation.

Warehouses



- Temperature monitoring system
- Alarms for over temperature or under temperature
- Emergency generator back-up
- Temperature mapping and validation

Weighing and sampling areas.



Weighing and sampling areas



Sampling of materials such as starting materials, primary packaging materials and products, should be carried out in the same environmental conditions that are required for further processing of the product



Weighing and sampling areas



Weighing areas:

- include a pre weighing staging area, personnel airlock, material airlock, weighing area with a containment booth, post-weighing staging area, washing area and provision for waste removal.
- logical flow of material and personnel.
- An appropriate number of AHUs,
- appropriate pressure differentials, containment, dust control, and rate of air exchange.





Weighing areas

- Weighing operation – in separate areas
- Appropriate design
- Provision for dust control
- Smooth, impervious, durable, easy-to-clean finishes
- Cleaning procedure and records
- Documentation eg. SOPs, logs and records



Weighing and sampling areas



the dust generated at the weighing location should be extracted through a perforated worktop



Weighing and sampling areas



In a weighing booth situation, the aim of the UDAF is to provide dust containment and operator protection.

The unidirectional flow velocity should be such that it does not disrupt the sensitivity of balances in weighing areas.



Weighing and sampling areas



The position in which the operator stands relative to the source of dust liberation and airflow should be determined to ensure that the operator is not in the path of an airflow that could lead to contamination of the product



UDAF

Perforated worktop


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Powder Container

Floor Scale

Weighing areas



Dispensary post-staging room 35 Pa
Staff flow
Change room
COB
25 Pa
Pallet
BIN BIN
BIN BIN
Airlock
35 Pa
Staff flow
Wash bay
25 Pa
BIN
Material flow
Perforated worktop
BIN
Table scale
Weigh booth
25 Pa
BIN
Airflow protection plenum
Floor scale
Return air shaft
Material flow
Dispensary pre-staging room 15 Pa

Weighing areas



Production passage
40 Pa
Dispensary post-staging room
35 Pa
Wash bay
Optional location
40 Pa
30 Pa
MAL
Change room
30 Pa
30 Pa
MAL
Change room
30 Pa
Weigh booth 1
20 Pa
Airflow protection plenum
Return air shaft
Weigh booth 2
20 Pa
Airflow protection plenum
Return air shaft
Broken bulk store
10 Pa
30 Pa
MAL
30 Pa
Wash bay
Optional location
30 Pa
MAL
30 Pa
Wash bay
Optional location
Dispensary pre-staging room
20 Pa
5 Pa
10 Pa
MAL
Warehouse area

Weighing areas



Production passage
30 Pa
Staff flow
Material flow
Dispensary post-staging room
20 Pa
Staff flow
Wash bay
Optional location
30 Pa
MAL
30 Pa
Change room
30 Pa
MAL
30 Pa
Change room
30 Pa
Weigh booth 1
20 Pa
Airflow protection plenum
Return air shaft
Weigh booth 2
20 Pa
Airflow protection plenum
Return air shaft
Broken bulk store
10 Pa
30 Pa
MAL
30 Pa
Wash bay
Optional location
30 Pa
MAL
30 Pa
Wash bay
Optional location
Staff flow
Material flow
Dispensary pre-staging room
20 Pa
5 Pa
10 Pa
MAL
Warehouse area

Sampling areas



Staff flow

Warehouse area

5 Pa

25 Pa

SCB

Change room

30 Pa

Wash bay

Perforated worktop

Return air shaft

Material flow

PTH

Material flow

Sampling booth

15 Pa

Airflow protection booth plenum

Sampling areas



Write-up worktop
Return air plenum
Change room
25 Pa
Wash bay
30 Pa
5 Pa
Warehouse area
APB (Airflow protection booth)
Sampling booth
15 Pa
Material flow
25 Pa
Entry MAL
25 Pa
Exit MAL
Material flow

MAL: material airlock.

Oral solid dosage forms

Oral solid dosage forms



A clean corridor concept is usually recommended for non-sterile oral solid-dosage form production areas, where there is then a higher pressure in the corridor compared to airlocks or production rooms.

This is to facilitate containment of dust and contaminants that may have been generated in production rooms

Oral solid dosage forms



- Correct directional air movement and a pressure cascade system can assist in preventing cross-contamination. The pressure cascade should be such that the direction of airflow is from the clean corridor into the cubicles, resulting in dust containment.
- The corridor should be maintained at a higher pressure than the cubicles, and the cubicles at a higher pressure than atmospheric pressure.





IPC (friability, hardness, dissolution, balance..), spare part store, washing area, bulk store, dispensed material staging

MF (RM, 1ry pack, intermediates..), PF, WF



Oral solid dosage forms



Production passage
30 Pa

COB
15 Pa
Female change room

COB
15 Pa
Male change room

Lobby
0 Pa

Female toilets
-10 Pa

-10 Pa
Male toilets

Unclassified zone

Oral solid dosage forms



Wash bay
25 Pa
Dirty equipment store
15 Pa
30 Pa
Production passage
Clean equipment store
45 Pa
Equipment drying
35 Pa
Material flow
Material flow
Material flow
Material flow
Material flow



Oral solid dosage forms



- For containment, consideration may also be given to having material airlocks (MALs) and personnel airlocks (PALs), where needed, for entry and exit of processing areas.

- Appropriately designed airlocks can assist in ensuring containment. Additional controls, such as pressure differentials between areas, an appropriate number of air changes in an area, and sufficient filtration of air, should be in place.



Oral solid dosage forms



Change room
25 Pa
Compression cubicle
15 Pa
Low level return air
Low level return air
Supply air grille
MAL
25 Pa
35 Pa
Production passage

Semisolids/Liquids





Rooms +ve to corridor

Liquids → preparation, (air blowing) filling →2 ry packaging

Semisolids→ preparation , filling (suppositories "cooling")

CIP?

Liquids/Semisolids



- Liquids, creams and ointments may be particularly susceptible to microbial and other contamination during manufacture. Therefore special measures must be taken to prevent any contamination.
- The use of closed systems for processing and transfer is recommended in order to protect the product from contamination.

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Thank you


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Pharmaceutical plants design

Lecture 2

Presented by: Dr Amal Adel

Content

Sterile area



•



General considerations



The production of sterile preparations should be carried out in clean areas, entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate standard of cleanliness and supplied with air that has passed through filters of the required efficiency.



General considerations



The various operations of component preparation (such as those involving containers and closures), product preparation, filling and sterilization should be carried out in separate areas within the clean area



General considerations



Flow Diagrams of raw materials to final product into the processing area of sterile pharmaceutical products should be established and, as the situation may require, appropriate disinfection and sterilization procedures should be implemented. Appropriate procedures are also necessary to prevent microbial invasion into working areas during a transfer of raw and other materials.

General considerations



Manufacturing operations are divided here into two categories:
— first, those where the product is terminally sterilized; and
— second, those which are conducted aseptically at some or all stages

Terminally sterilized production

Aseptic



Terminally Sterilized Product



- Terminal sterilization is a traditional method going back to the 19th century industry.
- For this method, most drug products are produced by mixing the ingredients to form the bulk drug product solution.
- Which is then filled into a container such as ampoule vial, ;tightly sealed with a rubber-type stopper or syringe plunger.
- Then sterilized the sealed container, usually with high heat in a chamber called a steam *autoclave*.
- Since the container is fully sealed prior to terminal sterilization, there is very little risk of contamination afterwards.

Terminally Sterilized Product



Terminal sterilization

sealed vial + autoclave = sterile drug


Terminally Sterilized Product



Components and most products should be prepared in at least a Grade D environment to ensure low microbial bioburden and particulate counts prior to filtration and sterilization. Where the product is at unusual risk of microbial contamination (e.g. because it actively supports microbial growth, must be held for a long period before sterilization, or is necessarily processed mainly in open vessels), the preparation should generally be done in a Grade C environment

Terminally Sterilized Product



Moist heat sterilization is the preferred sterilization process for „terminal sterilization

Terminal sterilization: Sterilization of finished pharmaceuticals in their final container in which an aqueous formulation is processed to provide a minimum probability of a non-sterile unit of 1 x 10-6





Terminally Sterilized Product



Classical sterilization techniques using saturated steam under pressure or hot air are the most reliable and should be used whenever possible. Other sterilization methods include filtration, ionizing radiation (gamma and electron-beam radiation), and gas (ethylene oxide, formaldehyde).

Terminally Sterilized Product



-The filling of products for terminal sterilization should generally be done in at least a Grade C environment.

(Grade A zone with at least a Grade C background).

Terminally Sterilized Product



for products that have been heat sterilized in their final containers,

consideration should be given to taking samples from that part of the

load that is potentially the coolest.

The sterility of the finished product is assured by validation of the sterilization cycle

in the case of terminally sterilized products

aseptic preparation



Asepsis is the condition that is free from pathogenic harmful bacteria,

viruses, fungi and parasites or harmful spores.

aseptic preparation



Sterilization by filtration is employed mainly for thermos-labile solutions. These may be sterilized by passage through sterile bacteria-retaining filters, e.g. membrane filters (cellulose derivatives, etc)

aseptic preparation



aseptic processing

Sterile Drug Product

Sterile Container

Sterile Closure

Sterile Filling Materials

→ Aseptic Processing = Sterile Final Product

aseptic preparation



When terminal sterilization is not an option, aseptic processing is used. **Each component (drug, container, closure, etc.) is individually sterilized first, then carefully assembled in a clean room to make the finished drug product in a manner that prevents contamination.**



aseptic preparation



Aseptic processing cannot provide the same quantitative level of sterility assurance as terminal sterilization, but it features several layers of control to minimize the risk of contamination.

Containers, closures, and filling materials go through their own validated sterilization cycles.

aseptic preparation



- Appropriate measures should be taken to avoid loss of solute by adsorption onto the filter and to prevent the release of contaminants from the filter.

- Suitable filters will prevent the passage of microorganisms, but the filtration must be followed by an aseptic transfer of the sterilized solution to the final containers which are then immediately sealed with great care to exclude any recontamination

aseptic preparation



- **Integrity tester**
- Usually, membranes of not greater than 0.22 µm nominal pore size should be used.
- To confirm the integrity of filters, both before and after filtration, a bubble point or similar test should be used, in accordance with the filter manufacturer's instructions. This test employs a prescribed pressure to force air bubbles through the intact membrane previously wetted with the product, with water, or with a hydrocarbon liquid.





- The integrity of the sterilized filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test..
- The integrity of critical gas and air vent filters should be confirmed after use.

aseptic preparation



- All filters, tubes, and equipment used "downstream" must be sterile.
- Filters capable of withstanding heat may be sterilized in the assembly before use by autoclaving at 121 °C for 15 - 45 minutes depending on the size of the filter assembly.
- The effectiveness of this sterilization should be validated.
- For filtration of a liquid in which microbial growth is possible, the same filter should not be used for procedures lasting longer than one working day.

aseptic preparation



- Operator gowning in an aseptic processing area typically consists of full coverage
- – no skin or hair is exposed – with sterilized coveralls, hoods, boots, goggles, and gloves.
- Operators are highly trained from how to put these gowns on to using proper aseptic techniques to avoid contamination.
- Each operator must pass certification testing before they are allowed to participate in aseptic activities.

aseptic preparation



Aseptic processing

- for products that have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant interruption of work

- The sterility of the finished product is assured by by “media simulation” or “media fill” runs for aseptically processed products.



aseptic preparation



- Validation of aseptic processing should include a process simulation test using a nutrient medium (media fill). Selection of the nutrient medium should be made based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilization of the nutrient medium.





- The handling of sterile starting materials and components, unless subjected to sterilization or filtration through a microorganism retaining filter later in the process, should be undertaken in a Grade A environment with a Grade B background.





- The handling and filling of aseptically prepared products, as well as the handling of exposed sterile equipment, should be undertaken in a Grade A environment with a Grade B background.

aseptic preparation



- The interval between the washing and drying and the sterilization of components, bulk-product containers and equipment, as well as between sterilization and use, should be as short as possible and subject to a time limit appropriate to the validated storage conditions.
- **Tanks CIP/SIP**
- **(garments- machine parts) washing , sterilization**
- **Sterilization holding time, sampling locations**

aseptic preparation



The transfer of partially closed containers, as used in freeze-drying, before stoppering is completed, should be undertaken either in a Grade A environment with a Grade B background or in sealed transfer trays in a Grade B environment.



aseptic preparation



The preparation and filling of sterile ointments, creams, suspensions and emulsions should be undertaken in a Grade A environment with a Grade B background when the product is exposed and is not subsequently filtered.

aseptic preparation



Grade A and B areas should be designed so that all operations can be observed from outside



aseptic preparation



Components, bulk-product containers, equipment, and any other

articles required in a clean area where aseptic work is in progress, should

be sterilized and wherever possible passed into the area through double ended

sterilizers sealed into the wall.

Other procedures that prevent the introduction of contamination may be acceptable in

some circumstances. (DPb, wrapping, sanitization “contact time”, SOPs)

General considerations



Pre-sterilization preparation of glass containers usually involves a series of wash and rinse cycles. These cycles serve an important role in removing foreign matter.

Subjecting glass containers to dry heat generally accomplishes both sterilization and depyrogenation .

Depyrogenation







General considerations



Storage Details of Dried and Sterilized Items

The sterilized rubber stoppers, the pre-sterilized rubber stoppers, the sterilized Aluminum seals and equipment and accessories for sealing, Sterilized vessel for manufacturing, Sterilized vessel load for filtration, Sterilized equipment and accessories for manufacturing, Sterilized equipment and accessories for filtration, filling and capsule filter, Sterilized lyo trays and lyo frames are stored under LAF in filling area.



General considerations



There should be a clear means of differentiating products that have not been sterilized from those which have. Each basket, tray, or other carrier of products or components should be clearly labelled with the name of the material, its batch number and an indication of whether or not it has been sterilized. Indicators such as autoclave tape may be used where appropriate to indicate whether or not a batch (or sub-batch) has passed through a sterilization process, but they do not give a reliable indication that the batch is in fact sterile.

Loading/unloading (receiving)



General considerations



- Drains and sinks should not be installed in areas of Grade B or higher. If drains are placed in other support areas (Grade C or D), certain contamination preventive measures that enable easy cleaning and disinfection should be considered.

General considerations



- warning system should be operated to indicate failure in the air supply. Indicators of pressure differentials should be fitted between areas where this difference is important, and the pressure differentials should be regularly recorded and failure alarmed.

General considerations



A conveyor belt should not pass through a partition between a Grade A or B clean area and a processing area of lower air cleanliness, unless the belt itself is continuously sterilized (e.g. in a sterilizing tunnel).



General considerations



- If the cleanliness level of direct support areas is specified as Grade B, gowning rooms should be portioned into entry and exit blocks.

- Personnel entry into filling and sealing areas should be kept to a minimum.

General considerations



Sterile gowning:

- Identification for each gown
- Validated sterilization cycles (loads)
- Washing, drying ,Check (integrity, zipper, ..),sterilization (number of sterilization cycles), log book



General considerations



General considerations



- Clothing used in clean areas should be laundered or cleaned in such a way that it does not gather additional particulate contaminants that can later be shed.
- Separate laundry facilities for such clothing are desirable. If fibers are damaged by inappropriate cleaning or sterilization, there may be an increased risk of shedding particles.
- Washing and sterilization operations should follow standard operating procedures.



General considerations



- Major items of equipment associated with hydraulic, heating and cooling systems, e.g. such as those associated with Blow-Fill-Seal equipment should, where possible, be located outside the filling room.





- equipment fittings and services should be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area.
- Equipment that has to be taken apart for maintenance should be re-sterilized after complete reassembly

General considerations



The various operations of component preparation (such as those involving containers and closures), product preparation, filling and sterilization should be carried out in separate areas within the clean area.

Vials , ampoules → Enter through **depyrogenation** tunnel or after depyrogentation in oven →filling area

Rubber → Enter through autoclave → filling area

Caps → A/L → capping area

→Autoclave→ filling &capping

General considerations



- The container closure system for aseptically filled vials is not fully integral until the aluminum cap has been crimped into place on the stoppered vial. Crimping of the cap should, therefore, be performed as soon as possible after stopper insertion.

- As the equipment used to crimp vial caps can generate large quantities of non-viable particulates, the equipment should be located at a separate station equipped with adequate air extraction.

General considerations



Containers should be closed by appropriately validated methods.

Containers closed by fusion, e.g. glass or plastic ampoules, should be subject to 100% integrity testing.

Samples of other containers should be checked for integrity according to appropriate procedures..



General considerations



Weighing and preparation processes of pharmaceutical solution, etc. are usually conducted in Grade C areas. If certain contamination-preventive measures are implemented by, for example, processing in closed systems, the preparation of pharmaceutical solution may be performed in a Grade D area.

General considerations



Receiving & weighing of raw materials → ampoule receiving

Solution preparation

Solution filtration

ampoule & sterilization

Ampoule Filling & Sealing

Product Sterilization

Visual Inspection

ampoule Labeling

Packaging

General considerations



Recommended limits for microbial contamination[a]

Grade	Air sample (CFU/m3)	Settle plates (diameter 90 mm) (CFU/4 hours)[b]	Contact plates (diameter 55 mm) (CFU/plate)	Glove print (5 fingers) (CFU/glove)
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	–
D	200	100	50	–

CFU, colony-forming units.

[a] These are average values.

[b] Individual settle plates may be exposed for less than 4 hours.



General considerations



Only the minimum number of personnel required should be present in cleanrooms. The maximum number of operators in cleanrooms should be determined, documented and validated during activities such as initial qualification and *aseptic process simulations*, so as not to compromise sterility assurance. This is particularly important during aseptic processing.

General considerations



<u>Manual inspection</u>

suitable and controlled conditions of illumination and background.

General Consideration



Visual inspection

General considerations



Manual inspection

The qualification should be undertaken using appropriate samples from the manufacturer's defect library sets and taking into consideration worst case scenarios (e.g. inspection time, line speed where the product is transferred to the operator by a conveyor system, container size or fatigue at the end of shift) and should include consideration of eyesight checks. Operator distractions should be minimized and frequent breaks, of an appropriate duration, from inspection should be taken.

Isolators and Rabs



RABS gloves used in Grade A zone should be sterilized before installation (environmental monitoring)

The frequency of glove replacement should be defined

For RABS and isolator systems, decontamination methods should be validated and controlled within defined parameters.(including sporicidal agent)

Isolators and RABs



- -The critical zone of the RABS or isolator used for aseptic processes should meet Grade A requirements.
- -For RABS used for aseptic processing, the background environment should meet at least Grade B.
- -The materials used for glove systems (for both RABS and isolators), as well as other parts of an isolator, should be demonstrated to have good mechanical and chemical resistance.
- -leak testing of the glove system should be performed. The testing should be performed at defined periods, at a minimum at the beginning and end of each batch

Isolators and Rabs



Aseptic process



Filtration alone is not considered sufficient when sterilisation in the final container is possible.

If product cannot be sterilised in the final container, solutions or liquids can be filtered through a filter of nominal pore size of 0.22 micron or less into a previously sterilised container

-Such filters can remove most bacteria and moulds but NOT all viruses or mycoplasmas

-Consideration should be given to complementing the filtration process with some degree of heat treatment

General Consideration



Sterilising (Membrane/Cartridge/Disc) filters are used in pharmaceutical manufacture for:

-Bulk Product Filtration

-Gas Filters

-Vent Filters



Aseptic process



For products which do not undergo terminal sterilisation, a second further filtration (double filtration) is recommended:

-immediately prior to filling

-as close as possible to the filling point



Lyophilization



What is Lyophilization

•a product after it is frozen and placed under a vacum, allowing the ice to change directly from solid to vapor without passing through a liquid phase.

•unique, and interdependent processes; freezing, primary drying (sublimation), and secondary drying (desorption).



Lyophilization



The steps required to lyophilize a product in a batch process can be summarized as follows:

Formulation

Loading / Container (Vials)

Freezing (Thermal Treatment) at atmospheric pressure

Primary Drying (Sublimation) under vacuum

Secondary Drying (Desorption) under vacuum

Backfill & Stoppering (for product in vials) under partial vacuum

Removal of Dried Product from Freeze Dryer



Lyophilization



Vial washing → Vial sterilization and depyrogenation → Vial filling/ stoppering → Lyophilization → Capping → Final packing

Lyophilization



Vial washing → Vial sterilization and depyrogenation → Vial filling/ stoppering → Lyophilization → Capping → Final packing

Closure integrity testing



Validation of the closure system by filling the container with sterile growth medium and inserting the container in a broth containing approx. 10^6 cfu/ml of a suitable micro-organism. The container is removed after submersion for a recognised period of time, disinfected and then incubated for 14 days. Growth would indicate a failure of the closure system.



Hazardous products



Facilities should be designed:

— to ensure quality of product;

— to protect the operators from possible harmful effects of products containing hazardous substances; and

— to protect the environment from contamination and thereby protect the public from possible harmful effects of products containing hazardous substances.

Hazardous products



Generally, Where possible products should be manufactured in closed systems

Hazardous products



Product Protection (Hazardous and General):

-Facility layout

-HVAC AHU (Safe Filter Changing –HEPA on return)

-Cleaning System (Dust collector)

Personnel protection (ADE Study)

-Personnel Gowning System

-Environmental protection

-Layout

-HVAC Exhaust HEPA filter

-Effluent Treatment (waste treatment unit)

-Personnel Decontamination System

Hazardous products





The production of certain products containing hazardous substances should generally be conducted in separate, dedicated, self-contained facilities.

In general these manufacturing facilities should be regarded as containment facilities.

Hazardous products



- Appropriate facility design and layout, with the emphasis on safely containing the materials being handled.

- Manufacturing processes using closed systems or barrier technology enhance operator and product protection







Hazardous products



An air shower comprises an airlock where high velocity air is supplied through air nozzles (e.g. from the sides of the airlock) in order to dislodge dust particles. Air extraction grilles (e.g. at low level) should draw the air away and return it to the filtration system.

Hazardous products



- Air filtration of the supply air and return or exhaust air should comply with the same filtration standards as used in the manufacturing facility. Normally the fan should be activated by opening the door as the operator enters the shower, with a timing device on the exit door interlock to allow sufficient time for the decontamination process to be effective.

Hazardous products



barrier technology

A system designed to segregate people from the product, contain contaminants or segregate two areas, which could be a barrier isolator (BI) or a restricted access barrier system (RABS):

- A BI is a unit supplied with high-efficiency particulate air (HEPA) filtered air that provides uncompromised continuous isolation of its interior from the external environment, including surrounding clean room air and personnel.
- A RABS is a type of barrier system that reduces or eliminates interventions into the critical zone. In practice, its level of contamination control is less than that of a barrier isolator.

Hazardous products



- Neither the product nor its residues should be allowed to escape into the atmosphere or to be discharged directly to normal drainage systems.

- The external atmosphere and the public in the vicinity of the facility should be protected from possible harm from hazardous substances.

- If liquid effluent poses a safety or contamination risk, the effluent should be treated before being discharged to a municipal drain.


Hazardous products



- The premises should be designed and constructed to prevent the ingress or egress of contaminants. In drawing up the facility design, attention should be paid to the level of containment provided by the equipment.
- The link between the interior and exterior of the premises should be through airlocks (PAL and/or MAL), changing rooms, pass boxes, pass through hatches, decontamination devices, etc.

Hazardous products



These entry and exit doors for materials and personnel should have an interlock mechanism or other appropriate system to prevent the opening of more than one door at a time.

The changing rooms should have an arrangement with a step-over bench. The facilities on the exit side should incorporate showers for the operators.

The premises should be laid out and designed so as to facilitate the required pressure cascades and containment.

Hazardous products



The premises (and equipment) should be appropriately designed and installed to facilitate cleaning and decontamination.

The flow of people and products should be clearly marked on the layouts and plans.

Plans should describe the ventilation systems, indicating inlets and outlets, in relation to other facility air inlet and outlet points.

Hazardous products



-The facility should be a well-sealed structure with no air leakage through ceilings, cracks or service areas.

-Areas of the facility where exposed product presents a risk should be maintained at a negative air pressure relative to the environment.



Hazardous products



- Air should be exhausted to the outside through HEPA filters and not be recirculated except to the same area, and provided that a further HEPA filtration stage is applied to the return air.

Hazardous products



Where possible, single-pass air-handling systems with no recirculation should be provided.

• Exhaust air or return air should be filtered through a safe-change or bag in-bag-out filter housing. The filter housing should contain pre-filters and HEPA filters, both of which should be removable with the safe bagging system.

Hazardous products



the operators leaving the containment area should pass through a decontamination system, e.g. air showers or a mist shower system, to assist with removing or controlling dust particles on their garments.

Operators should follow this route before de-gowning to use the ablutions or canteen facilities. All garments leaving the facility for laundering should be safely bagged. Appropriate means for protecting laundry staff and prevention of contamination of other garments from non-hazardous facilities should be in place

Hazardous products



appropriate measures should be taken to prevent airflow from the primary packing area (through the conveyor “mouse hole”) to the secondary packing area.

This could be overcome by having a pass-through chamber over the “mouse hole”, which is maintained at a negative pressure to both primary and secondary packing.

Hazardous products



EXTRACTION

Supply Air

Supply Air

PRIMARY PACKING

(NEGATIVE PRESSURE ---)

SECONDARY PACKING

(NEGATIVE PRESSURE --)

(NEGATIVE PRESSURE -)

Extract Air

Supply Air

Hazardous products



-providing an emergency power supply, e.g. diesel generators, to ensure that safe operation of the premises and systems can be maintained at all times.

Hazardous products



the return air passes through two sets of HEPA filters in series, i.e. the return air filters in the safe change housing and the supply air HEPA filters.

The supply air HEPA filters could either be located in the AHU or terminally located at the supply diffusers, depending on the clean room classification of the facility.

Safe change or bag-in-bag-out filter housings should be suitably designed to provide operator protection and to prevent dust from the filters entering the atmosphere when filters are changed.


Hazardous products



For dusty return, air pre-filtration may also be required to prolong the life of the HEPA filters. The pre-filtration filters should also be removable through the bag-in-bag-out method.



Hazardous products



For exhaust systems where the discharge contaminant is considered particularly hazardous, two banks of HEPA filters in series should be considered to provide additional protection should the first filter fail.



Hazardous products



All filter banks should be provided with pressure differential indication gauges to indicate the filter dust loading and remaining lifespan of the filters.

Hazardous products



Monitoring of filters should be done at regular intervals to prevent excessive filter loading that could force dust particles through the filter media, or could cause the filters to burst, resulting in ambient contamination.

Computer-based data monitoring systems may be installed to monitor filter condition.

Filter pressure gauges should be marked with the clean filter resistance and the change-out filter resistance.



Hazardous products



All exhaust systems from the facility, including dust extraction systems, vacuum system exhaust, fluid bed drier exhaust and coating pan exhaust, should be passed through safe change filter housings before being exhausted to the atmosphere.



Hazardous products



All exhaust points outside the building should be located as far as possible from air entry points, and exit points should be at a high level to minimize the possibility of re-entrainment of exhaust air. Dominant and seasonal wind directions should be taken into account when positioning exhaust and supply points

Hazardous products



Where excessively dust air is handled, a dust collector should be considered, with the dust collector being located in an enclosed room maintained at a negative pressure.

Access control, maintenance staff, personal protection equipment (PPE) and breathing air systems should then be provided to protect the operators during removal of dust from the collector bins.

Hazardous products



Portable vacuum cleaners and portable dust collectors should be fitted with H13 HEPA filters. These types of units should be emptied and cleaned in a room which is under negative pressure relative to the environment. Personnel should be provided with suitable PPE.

Records of the safe disposal of all contaminated filters and dust should be kept.

Hazardous products



Liquid and solid waste effluent should be handled in such a manner as not to present a risk of contamination to the product, personnel or to the environment.

All effluent should be disposed of in a safe manner, and the means of disposal should be documented. Where external contractors are used for effluent disposal they should have certification authorizing them to handle and treat hazardous products.

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Equipment Qualification & validation

Presented By : Dr Nermine Mohamed

Content

1. Introduction to Equipment
2. Qualification & Validation Definition
3. Qualification Stages
4. Re-Qualification & Re-Validation

Equipment Qualification & Validation



Introduction

Equipment must be:

- located
- designed
- Constructed
- adapted
- maintained

to suit their intended use.



Equipment Qualification & Validation



Equipment layout and design must aim:

- to minimize risks of error
- to permit effective cleaning
- to permit effective maintenance

And to avoid:

- cross-contamination
- dust and dirt build-up
- any adverse effect on the quality of products

Equipment Qualification & Validation



*Closed equipment used when possible.

*Open equipment, or when equipment opened, precautions taken to prevent contamination.

*Non-dedicated equipment cleaned according to validated cleaning procedures between different products.

*Current drawings of critical equipment and support systems maintained .

Equipment Qualification & Validation



Equipment Qualification & Validation



Pipes and piping



Fixed pipework:

- Clearly labelled
- Indicate contents
- Direction of flow

Service piping

- Adequately marked.
- Non-interchangeable connections or adaptors for dangerous gases and liquids.

Equipment Qualification & Validation



Balances and Measuring Equipment

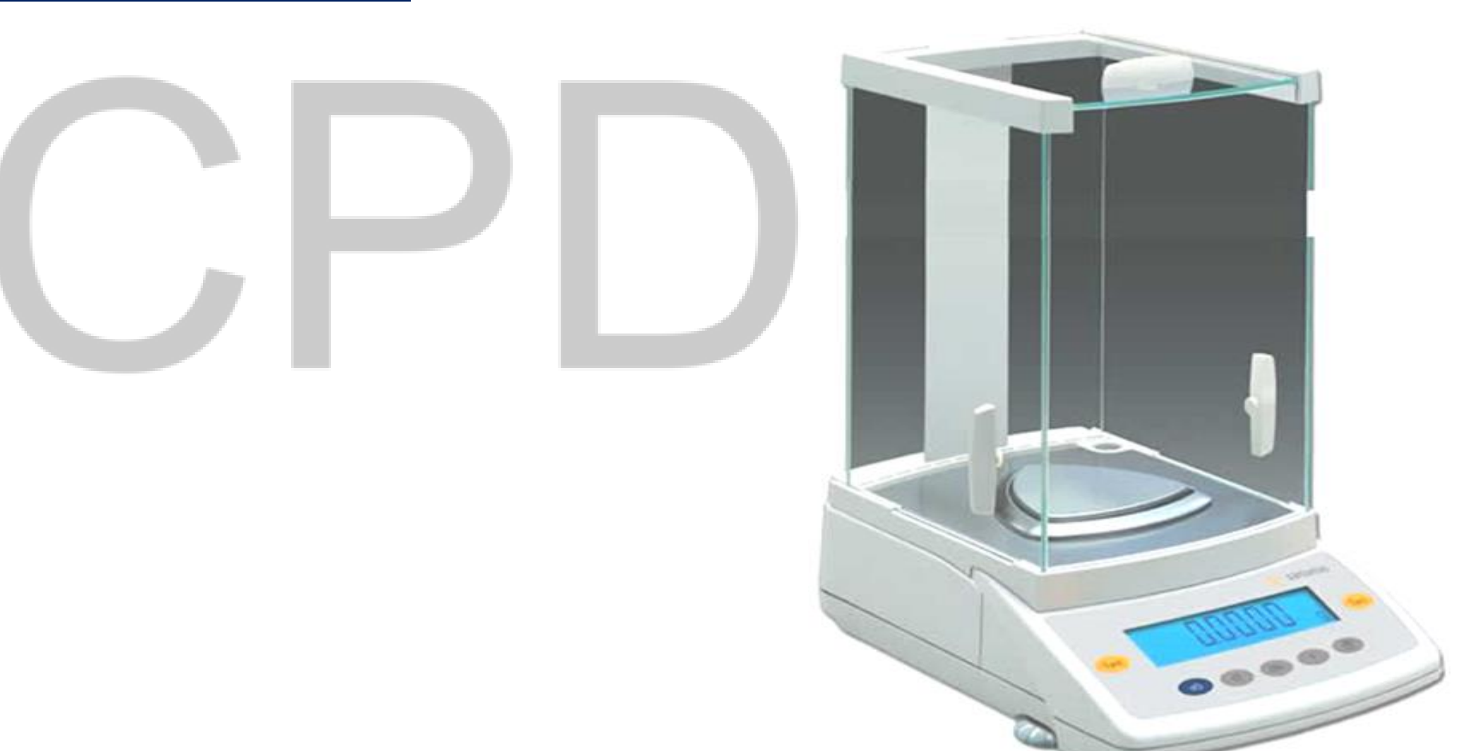
*Appropriate range
*Precision

Available to:

* Production
* Quality control

Calibrated

*Scheduled basis
*Checks
*Records maintained





Production equipment

No hazard to the products

- Suitable non-reactive materials
- Non additive
- Not absorptive

Defective equipment

- Removed
- Labelled

Equipment Qualification & Validation



*<u>***Washing and cleaning equipment:***</u>

- Manual

-Clean in place (CIP), Steam in place (SIP)

- Not the source of contamination



Equipment Qualification & Validation



Qualification Definition:



Documented evidence that premises, systems or equipment are able to achieve the predetermined specifications when properly installed, and/or work correctly and lead to the expected results.

Equipment Qualification & Validation



<u>Validation Definition:</u>





* Action of proving and documenting that any process, procedure or method actually and consistently leads to the expected results.



Equipment Qualification & Validation



Relationship between validation and qualification:

*In general, qualification and validation follow similar underlying principles. The term "qualification" is normally used, for example, for equipment and utilities, and "validation", for example, for systems, methods and processes.

*Qualification normally precedes validation.





Responsibility for Qualification and Validation

*The responsibility for qualification and validation in pharmaceutical manufacture is a multi-disciplinary one.

* The Production and Quality Control departments, Quality Assurance, other departments, like Engineering and Research and Development as well as Contractors are usually involved in the programme.

Equipment Qualification & Validation



Principle :



-In principle, premises, systems, utilities and equipment should be appropriately designed, installed, qualified, operated, cleaned and maintained, to suit their intended purpose.

Equipment Qualification & Validation



*Products should be produced and controlled using qualified equipment and instruments.

*Qualification should be executed by trained personnel & Training records should be maintained.



Equipment Qualification & Validation



*Where appropriate new premises, systems, utilities and equipment should be subjected to all stages of qualification.

*This includes the preparation of user requirements specification (URS), design qualification (DQ),(FAT) , (SAT), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).

Equipment Qualification & Validation



*Where it is decided that not all stages of qualification are required, justification should be provided.

*Qualification should be done in accordance with predetermined and approved qualification protocols.

*The protocol should specify the prerequisites and test details, including acceptance criteria.





A qualification report prepared at the completion of each stage of qualification (installation/operational/performance) should include the following:

- test results, including supporting calculations, documentation and raw/original data.
- test failures.
- recommendations and justification for issue resolution.
- conclusions.

Equipment Qualification & Validation



*Equipment should be released for routine use only once there is documented evidence that the qualification has been successful.

*Certain stages of the qualification may be done by a supplier or a third party, subject to the conditions and responsibilities as defined in writing and agreed between the parties.

Equipment Qualification & Validation



*All relevant SOPs for operation, maintenance , Cleaning and calibration should be prepared during qualification.

*Normally, qualification should be completed before process validation is performed.

Equipment Qualification & Validation



* Major equipment and critical utilities and systems, however, may require URS, DQ, IQ, OQ and PQ.

QUALIFICATION APPROACH

URS
FAT
OQ
DQ
IQ
PQ
Change Control



Equipment Qualification & Validation



1-User requirement specifications:

-Manufacturers should prepare a document that describes the requirements for the item (such as system for a utility, or equipment) to be sourced.





User Requirement Specifications

URS No.	Subject	Acceptance Criteria	Priority
URS-001	Number of punch stations	Not less than 6	Mandatory
URS-002	Punch type	EU 1"/ TSM 1"	Mandatory
URS-003	Die type	D	Mandatory
URS-004	Max. Main compression force (KN)	Not less than 40	Mandatory
URS-005	Max. Tablet diameter (mm)	Not less than 25	Mandatory
URS-006	Max. filling depth (mm)	Not less than 18	Mandatory
URS-007	Max. tablet thickness (mm)	Not less than 8	Mandatory
URS-008	Upper punch penetration depth (mm)	1 - 4	Mandatory
URS-009	Pitch circle diameter (mm)	Not less than 120	Mandatory
URS-010	Turret speed (rpm)	5 - 40	Mandatory
URS-011	Tablet output (tabs/h)	Up to 19000	Mandatory
URS-012	Machine dimension	NMT (110 X 110 X 220) L X W X H	Mandatory
URS-013	Tablet tooling requirements	Capable to produce 6.5 mm round concave tablets, lower side embossed "M" and the upper embossed "A".	Mandatory
URS-014	Tablet tooling requirements	Capable to produce 8 mm round concave tablets, lower side embossed "M" and the upper embossed "A".	Mandatory
URS-015	Tablet tooling requirements	Capable to produce 9 mm round concave tablets, lower side embossed "M" and the upper embossed "A".	Mandatory
URS-016	Tablet tooling requirements	Capable to produce 11 mm round concave tablets, lower side embossed "M" and the upper embossed "A".	Mandatory

Equipment Qualification & Validation



Documentation Requirements

URS No.	Subject	Acceptance Criteria	Priority
URS-022	User Manual	Should be available in English language.	Mandatory
URS-023	Mechanical drawing	Should be available in English language.	Mandatory
URS-024	Electrical Drawing	Should be available in English language.	Mandatory
URS-025	Manual for critical Parts	Should be available in English Language.	Mandatory
URS-026	List of spare parts	Should be available in English language.	Mandatory
URS-027	List of alarms	Should be available in English language.	Mandatory
URS-028	Maintenance manual and schedule	Should be available in English language.	Mandatory
URS-029	List of component	Should be available in English language.	Mandatory
URS-030	Cleaning procedure	Should be described in the manual	Mandatory
URS-031	MSDS for lubricator oil	Should be available in English language.	Mandatory
URS-032	Inspection report For the Upper and lower punches and Die	Should be available in English language.	Mandatory
URS-033	Certificate of analysis and testing for materials of tool steel	Should be available in English language.	Mandatory
URS-034	Certificates for material of construction of contact parts and non-contact parts for the machine	Should be available in English language.	Mandatory
URS-035	Calibration Certificates traceable to NIST standard	Should be available in English language.	Mandatory

Equipment Qualification & Validation



Software & Data Requirements

URS-040	Operating Software	The system shall operate with a minimum of operator involvement and include a graphical user interface (GUI) located at the equipment for the purpose of entering and/or displaying operational information including the following: 1- Total run counter and time.	Mandatory
URS-041	Operating Software	2- Indicator for machine status. (Working, Ready, Alarm)	Mandatory
URS-042	Operating Software	3- Turret Speed.	Mandatory
URS-043	Operating Software	4- Feeder Control.	Mandatory
URS-044	Operating Software	5- Dust collector Control.	Mandatory
URS-045	Operating Software	6-Alarm screen and alarm history.	Mandatory
URS-046	Operating Software	7- Control the main penetration depth.	Mandatory
URS-047	Operating Software	8- Control the main thickness.	Mandatory
URS-048	Operating Software	9- Control the filling depth.	Mandatory
URS-049	Operating Software	10- Report summary for all settings	Mandatory
URS-050	Backup and retrieval system	Availability of backup and retrieval for data.	Desirable
URS-051	Audit trail	Availability of audit trail	Desirable
URS-052	E-Signature	Availability of Electronic signatures	Desirable
URS-053	Lay-out of reports	Free adjustment	Desirable
URS-054	Groups of users and levels	Availability of assigning Privileges and rights for each group based of its level.	Desirable





Training Requirements

URS No.	Subject	Acceptance Criteria	Priority
URS-055	Training	Training video on , installation ,Operation and maintenance if applicable.	Desirable

Equipment Qualification & Validation



Engineering Requirements

URS No.	Subject	Acceptance Criteria	Priority
URS-056	Main electricity and grounding	Three phase, 380 volt and the voltage between each phase and the ground to be 220 volt.	Mandatory
URS-057	The control of the machine	The machine must be controlled by PLC	Mandatory
URS-058	The power of the main motor	Must be controlled by a frequency converter	Mandatory
URS-059	The power of the feeder motor	Must be controlled by a frequency converter	Mandatory
URS-060	Electrical wiring diagram and mechanical manual	Each electrical and mechanical part must be identified by symbols and clarified by its written function.	Mandatory
URS-061	Online inspection by supplier in case of software failure through the internet	inspection by network	Mandatory
URS-062	Trouble shooting	Alarm screen indicates the cause of any defected or damaged part	Mandatory
URS-063	Emergency	Presence of emergency stop button beside the main screen to be easily used.	Mandatory
URS-064	Dust collector	Shall be present and connected properly	Mandatory

Equipment Qualification & Validation



Environmental & Safety Requirements

URS No.	Subject	Acceptance Criteria	Priority
URS-065	Working range for Temperature	Shall operate between 15 – 40 °C effectively	Mandatory
URS-066	Working range for Relative Humidity	Shall operate between RH% 30 – 80 % effectively	Mandatory
URS-067	Emergency	Presence of emergency stop button beside the main screen to be easily used.	Mandatory
URS-068	Grounding connection	Shall be present	Mandatory
URS-069	Alarms - Pushed emergency stop	Shall be present	Mandatory
URS-070	Alarms - Main motor trip	Shall be present	Mandatory
URS-071	Alarms - Dust collector alarm	Shall be present	Mandatory
URS-072	Alarms - Main pressure overload	Shall be present	Mandatory
URS-073	Alarms - Opened doors	Shall be present	Mandatory
URS-074	Alarms - Filling depth over range	Shall be present	Mandatory
URS-075	Alarms - Main thickness over range	Shall be present	Mandatory
URS-076	Alarms - Opened main shaft cover	Shall be present	Mandatory



2- Design qualification: (DQ):

- DQ should provide documented evidence that the design specifications were met and are in accordance with the URS.

Equipment Qualification & Validation



3- Installation qualification: (IQ)

-Utilities and equipment should be correctly installed, in an appropriate location.

-There should be documented evidence of the installation. This should be in accordance with the IQ protocol, which contains all the relevant details.

-IQ should include identification and installation verification of relevant components identified (e.g. services, controls and gauges).



3- Installation qualification: (IQ)

-Identified measuring, control and indicating devices, should be calibrated on site, unless otherwise appropriately justified.

-The calibration should be traceable to national or international standards. Traceable certificates should be available.

-The outcome of the IQ should be recorded in the conclusion of the report, before OQ is started.

Equipment Qualification & Validation



3- Installation qualification: (IQ)

- **At this stage** : new equipment & the preventive maintenance requirements should be added to the preventive maintenance schedule of the manufacturer.

- Draft document for cleaning is developed from equipment supplier specification & should be finalized at the operation qualification & verified at the performance qualification stage.





3- Installation qualification: (IQ)

Installation qualification report Should Include details, e.g.:

-The supplier and manufacturer.
-System or equipment name, model and serial number.
-Date of installation.
-Spare parts, relevant procedures and certificates.

Equipment Qualification & Validation



Format for an installation qualification protocol and report[a]

Validation protocol ________ **Installation Qualification** ________ **Page** _____ **of** _____
Title: ______________ **Name and address of site:** ________________________________

Validation Protocol # ______________________ IQ Protocol number: ______
Title: ______________________________
Protocol written by: ______________________
Protocol approved by: ______________________ Date: ____________
QA Approval: ______________________ Date: ____________

Objective
To ensure that _______________ (system/equipment) installed conforms to the purchase specifications and the manufacturer details and literature, and to document the information that ______________________ (system/equipment) meets its specifications.
Equipment inventory number: ______________________________

Scope
To perform installation qualification as described in this IQ protocol at the time of installation, modification and relocation.

Responsibility
_______________ (post/person) overseeing the installation will perform the qualification and records results.
_______________ (post/person) will verify results and write the report.
Quality Assurance will review and approve the IQ protocol and report.

[a] This format is used for training purposes and reflects some of the possible contents for an installation qualification protocol.

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Format for an installation qualification protocol and report (continued)[a]

Validation protocol ________ **Installation Qualification** ________ **Page** _____ **of** _____
Title: ______________ **Name and address of site:** ________________________________

System/Equipment ______________________ **Code no.:** ______________

a. Description of the system/equipment being installed: general description of the function and the main components.
____

b. List of the main components:
1. ______________ Code no.: ______________
2. ______________ Code no.: ______________
3. ______________ Code no.: ______________
4. ______________ Code no.: ______________

c. Description of supporting utilities (e.g. piping, connections, water supply)
1. ______________ Code no.: ______________
2. ______________ Code no.: ______________
3. ______________ Code no.: ______________
4. ______________ Code no.: ______________

Procedure
1. Prepare a checklist of all components and parts, including spare parts according to the purchase order and manufacturer's specifications.
2. Record the information for each actual part, component, item of auxiliary equipment, supporting facilities, and compare with the manufacturer's specifications.
3. Record any deviations to the system/equipment.
4. Prepare a deviation report including justification of acceptance and impact on the function.
5. Prepare an IQ report.[b]
6. Submit the report to QA for review and approval.

[a] This format is used for training purposes and reflects some of the possible contents for an installation qualification protocol.
[b] As a minimum, the IQ report should include the date of initiation of the study, date completed, observations made, problems encountered, completeness of information collected, summary of deviation report, results of any tests, sample data (if appropriate), location of original data, other information relevant to the study, and the conclusion on the validity of the installation.

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Equipment Qualification & Validation



INSTALLATION QUALIFICATION PROTOCOL (IQ)
TABLET PRESS 3200i Ser.No.:

4.4 3200i TABLET PRESS STANDARD OPERATING PROCEDURES

4.4.1 Operation

List the title and document number of the Fette Tablet Press operational procedures.

Title	Document No.
Operating instruction **(Ref.: binder 1)**	3119645

Acceptance Criteria: All required information are provided.

Performed By: ________________ Date: ________________

Reviewed By: ________________ Date: ________________

INSTALLATION QUALIFICATION PROTOCOL (IQ)
TABLET PRESS 3200i Ser.No.:

4.4.4 Calibration Procedures

List the calibration procedures used on the Tablet Press.

Title	unit
Pressing forces **(Ref.: – external Calibration – Unit)**	Loading cell
Reference marks **(Ref.: Operating instruction binder 2, section 15)**	Encoder
Zero adjustment **(Ref.: Operating instruction, binder 2, section 15)**	Amplifier

Acceptance Criteria: All required information are provided.

Performed By: ________________ Date: ________________

Reviewed By: ________________ Date: ________________

Equipment Qualification & Validation



INSTALLATION QUALIFICATION PROTOCOL (IQ)
TABLET PRESS 3200i Ser.No.:

4.4 3200i TABLET PRESS STANDARD OPERATING PROCEDURES (continued)

4.4.5 Change Control Procedures

(Ref.: "CHANGE SHEET" in front of IQ–section)

List all modifications and changes on the press during IQ or later.

Title	Document No.	Date of modification

Acceptance Criteria: All required information are provided.

Performed By: ______________ Date: ______________
Reviewed By: ______________ Date: ______________

INSTALLATION QUALIFICATION PROTOCOL (IQ)
TABLET PRESS 3200i Ser.No.:

4.5 TABLET PRESS DRAWINGS ON CUSTOMER FILE

List all drawings on file and indicate where they are stored.

Drawing Title/Drawing No.	Revision No.	Storage Location

Acceptance Criteria: All required information are provided.

Performed By: ______________ Date: ______________
Reviewed By: ______________ Date: ______________





Factory acceptance test and site acceptance test:

-Where appropriate, FAT and SAT should be performed to verify the suitability of the system at site.

-This should be appropriately documented.

Equipment Qualification & Validation



-Factory acceptance test (FAT) :

- A test conducted, usually at the vendor’s premises, to verify that the system, equipment or utility, as assembled or partially assembled meets approved specifications.

-Site acceptance test (SAT):

*A test conducted at the manufacturer’s site of use, to verify that the system, equipment or utility, as assembled or partially assembled, meets approved specifications.





4- Operational qualification: (OQ)

- OQ should provide documented evidence that utilities, systems or equipment operate in accordance with operational specifications.

-Tests to confirm upper & lower operating limit.

- Operation controls, alarms, switches, displays and other operational components should be tested.

Equipment Qualification & Validation



-The completion of successful OQ should allow finalization of SOPs for the operation, Preventive maintenance, calibration, cleaning.

-Training of operators for the systems and equipment should be provided, and training records maintained.

- Systems and equipment should be released for routine use after completion of operational qualification.

Equipment Qualification & Validation



Format for an operational qualification protocol[a]

Validation protocol ________ **Operational Qualification** ________ **Page** _____ **of** _____
Title: ______________ **Name of Facility:** ______________________________

Validation Protocol # __________________ Operational Qualification ____________
Title ____

Protocol written by ______________________________________
Departmental Approval by ______________________________ Date __________
QA Approval by ______________________________ Date __________

Objective

To determine that the system/equipment operates according to specifications, and to record all relevant information and data to demonstrate that the system/equipment functions as expected.

Scope

To be performed after installation, modification or relocation, after the Installation Qualification has been completed.

Responsibility

Person responsible for operating the system/equipment will perform the qualification and record the information.

The supervisor will supervise the study, verify the completion of the records, write the deviation report and the Operational Qualification (OQ) Report.

Qualify Assurance will review and approve the OQ protocol and report.

[a] This format is used for training purposes and reflects some of the possible contents for an operational qualification protocol.

6.4 There should be documented records for the verification of operation (operational qualification report) to indicate the satisfactory operation.

6.5 Standard operating procedures for the operation should be finalized and approved.

6.6 Training of operators for the systems and equipment should be provided, and training records maintained.

6.7 Systems and equipment should be released for routine use after completion of operational qualification, provided that all calibration, cleaning, maintenance, training and related tests and results were found to be acceptable.

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Format for an operational qualification protocol (continued)[a]

Validation protocol ________ **Operational Qualification** ________ **Page** _____ **of** _____
Title: ______________ **Name of Facility:** ______________________________

Materials, Equipment, Documents

List of calibration equipment required (Chart 1).

Materials or supplies needed to perform the Operational Qualification

1 ______________________________ Code # __________
2 ______________________________ Code # __________
3 ______________________________ Code # __________
4 ______________________________ Code # __________
5 ______________________________ Code # __________
6 ______________________________ Code # __________

SOPs and datasheets for normal operations of the system under test (Chart 2).

Training records documenting that operators have been trained (Chart 2).

Manuals for equipment (Chart 2).

Procedure

Test and record calibration data for calibrating apparatus and instruments (Chart 1).

Test and record operative condition of control points and alarms (Chart 3).

Test and record outputs (Chart 4).

List of calibration requirements for the system under test and records of the calibration of the system (Chart 5).

Measure and record the results of specific challenge to the system in normal and worst case situation where appropriate (Chart 6).

Record any deviations to the procedures performed.

Prepare a Deviation Report including the justification of acceptance and impact on the operation.

Prepare an Operational Qualification Report. This should include date study initiated; date completed; observations made; problems encountered; completeness of information collected; summary of deviation report; results of control/alarm tests; sample data if appropriate; location of original data; other information relevant to the study; and conclusions on the validity of the equipment/system operations.

Submit QA for review and approval.

[a] This format is used for training purposes and reflects some of the possible contents for an operational qualification protocol.

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Equipment Qualification & Validation



PROTOCOL NO.:_______ **LOCATION:**____________________

MACHINE NO.:________ **DATE ASSIGNED:**_______________

TEST No.: 38 **TEST TITLE:** Slow gate delay

(A) OBJECTIVE

To demonstrate that, according to the manufacturer's specification, the slow gate will operate with the correct time delay as specified in parameter no. 68.

(B) DETAILED TEST PROCEDURE

1. Set parameter 68 to 10 seconds and record the value in table below.
2. Start the machine.
3. Use a calibrated stopwatch to take the time between the machine start and the activation of the slow gate and record the value in the table below.

CALIBRATION DATE OF STOPWATCH:_________________________

SPECIFIED VALUE	ACTUAL VALUE
__________sec	________sec

(C) ACCEPTANCE CRITERIA

The displayed time in the actual field of parameter 68 and the visually recorded time are within 15 % of each other.

The test results satisfy the acceptance criteria Yes ( ) No ( )

Record all test results that do not meet the Acceptance Criteria.

Performed By:_______________ **Date Performed:**____________

Reviewed By:________________ **Date Reviewed:**____________

PROTOCOL NO.:_______ **LOCATION:**____________________

MACHINE NO.:________ **DATE ASSIGNED:**_______________

TEST No.: 41 **TEST TITLE:** Drums – set quantity

OPTIONAL: availability YES ( ) NO ( )

(A) OBJECTIVE

To demonstrate that, according to the manufacturer's specification, the machine will stop after the number of drums on the loading center is filled, as specified in parameter no. 72.

(B) DETAILED TEST PROCEDURE

1. Rotate the loading center for station 1 to position 1.
2. Place empty drums on the loading center.
3. Set the parameter 16 to 1.
4. To reset the drum counter, press the letter O on the keyboard, enter a new batch No. and then press the enter button .
5. Set parameter 72 drums – set quantity to 5.
6. Start the machine.
7. After the machine has stopped, record the diagnose displayed on the monitor in parameter list B 1.

   DIAGNOSE 8302 IN B 1:____________________________

   DIAGNOSE 8303 IN B 2:____________________________
8. Verify the number of filled drums on the loading center with the specified number in parameter 72.

   9.Repeat step 1 to 8 for parameter list B 2. (station 2)

(C) ACCEPTANCE CRITERIA

The displayed number of drums in the actual field of parameter 72 and the visually counted number of drums on the loading center are the same.

The test results satisfy the acceptance criteria Yes ( ) No ( )

Record all test results that do not meet the Acceptance Criteria.

Performed By:_______________ **Date Performed:**____________

Reviewed By:________________ **Date Reviewed:**______________

Equipment Qualification & Validation



PROTOCOL NO.:_______ **LOCATION:_______________ __**

MACHINE NO.:________ **DATE ASSIGNED:_______________**

TEST No.: 40 – 1 **TEST TITLE: rotor after run**

OPTIONAL: availability YES ( ) NO ( )
(only applicable with option S548)

(A) OBJECTIVE

To demonstrate that, according to the manufacturer's specification, the rotor will operate with the correct timing as specified in parameter no. 70 rotor after run.

(B) DETAILED TEST PROCEDURE

1. Set parameter 70 to 10 seconds and record the value in table below.
2. Start the machine. Wait 10 seconds and stop the machine.
3. Use a calibrated stopwatch to take the time the fillomatic stop and the stop of the rotor and record the value in the table below.

CALIBRATION DATE OF STOPWATCH:___________________________

SPECIFIED VALUE	ACTUAL VALUE
__________sec	________sec

(C) ACCEPTANCE CRITERIA

The displayed time in the actual field of parameter 70 on parameter list D and the visually recorded time are within 10 % of each other.

The test results satisfy the acceptance criteria Yes ( ) No ( )

Record all test results that do not meet the Acceptance Criteria.

Performed By:_______________ **Date Performed:____________**

Reviewed By:_______________ **Date Reviewed:_____________**

PROTOCOL NO.:_______ **LOCATION:___________________**

MACHINE NO.:________ **DATE ASSIGNED:_______________**

TEST No.: 42 **TEST TITLE: Total drums / current**

OPTIONAL: availability YES ( ) NO ( )

(A)OBJECTIVE

To demonstrate that, according to the manufacturer's specification, the machine will count the number of drums on the loading center correctly and will display this number in the actual field of parameter 73.

(B) DETAILED TEST PROCEDURE

1. Rotate the loading center for station 1 to position 1.
2. Place empty drums on the loading center.
3. Set the parameter 16 to 1.
4. To reset the drum counter, press the letter O on the keyboard, enter a new batch No. and then press the enter button .
5. Set parameter 72 drums – set quantity to 5.
6. Start the machine.
7. After the machine has stopped, verify that the number of filled drums on the loading center and the number of drums displayed in the actual field of parameter 73 are the same.
8. Repeat step 1 to 7 for station 2.

(C) ACCEPTANCE CRITERIA

The displayed number of drums in the actual field of parameter 73 and the visually counted number of drums on the loading center are the same.

The test results satisfy the acceptance criteria Yes ( ) No ( )

Record all test results that do not meet the Acceptance Criteria.

Performed By:_______________ **Date Performed:____________**

Reviewed By:_______________ **Date Reviewed:____________**





5-Performance qualification : (PQ)
-PQ should include, but is not limited to, the following:

*Tests using production materials, qualified substitutes or simulated products proven to have equivalent behavior under operating conditions, with worst case batch sizes where appropriate.

*Tests covering the intended operating range of the intended process, unless documented evidence from the development phase confirming the operation range is available.

Equipment Qualification & Validation



-There should be records for the PQ (e.g. a PQ report), to indicate the satisfactory performance over a predefined period of time to prove consistency.

Equipment Qualification & Validation



Format for a performance qualification protocol (continued)[a]

Validation protocol ________ **Performance Qualification** ________ **Page** _____ **of** _____
Title: ____________________ **Name of facility:** ______________________________

Responsibility

Person responsible for operating the system or equipment will perform the qualification and record the information.

The supervisor will supervise the study, verify the completion of the records and write the Deviation Report and the Performance Qualification Report.

Qualify Assurance will review and approve the Performance Qualification Protocol and Report.

Materials, Equipment, Documents

SOPs for normal operations of the equipment or system under test (including data record forms, charts, diagrams materials and equipment needed). Attach copies.

SOP list:

____
____
____
____
____
____

SOPs specific for performance tests (including data record forms, charts, diagrams, materials and equipment needed, calculations and statistical analyses to be performed, and pre-determined specifications and acceptance criteria). Attach copies.

SOP list:

____
____
____
____
____
____

[a] This format is used for training purposes and reflects some of the possible contents for a performance qualification protocol.

Format for a performance qualification protocol (continued)[a]

Validation protocol ________ **Performance Qualification** ________ **Page** _____ **of** _____
Title: ____________________ **Name of facility:** ______________________________

Procedure

Equipment: Run normal procedure three times for each use (configuration or load) and record all required data and any deviations to the procedure.

Systems: Run for 20 consecutive working days, recording all required data and any deviations to the procedure.

Prepare the Summary Data Record Form(Chart 1).

Evaluation

Attach all completed, signed data record forms.

Complete the Summary Data Record Form (Chart 1).

Perform all required calculations and statistical analyses (Chart 2).

Compare to acceptance criteria (Chart 3).

Prepare Deviation Report including the justification of acceptance and impact on the performance.

Prepare a Performance Qualification Report: This should include: date study initiated; date completed; observations made; problems encountered; completeness of information collected; summary of deviation report; results of any tests; do results meet acceptance criteria; location of original data; other information relevant to the study; and conclusions on the validity of the equipment/system.

Submit Performance Qualification Document to QA for review and approval.

[a] This format is used for training purposes and reflects some of the possible contents for a performance qualification protocol.

Equipment Qualification & Validation



Group Activity:











Requalification
Defined schedule
Frequency based on Factors
Results of calibration maintenance, verification
Periodic
After change
Extent based on Risk assessment
Part of Change control procedure

Equipment Qualification & Validation



Re-qualification:

-Utilities, systems and equipment should be maintained in a qualified state. Any changes made to these should be managed through the change control procedure.

-Where a system or utility or equipment has not been used for an extended period of time, requalification may have to be considered.





Re-qualification:

*Factors such as the frequency of use, breakdowns results of operation, criticality, preventive maintenance, repairs(parts are replaced , calibration, Modification, re-location and verification may be considered.

Equipment Qualification & Validation



Re-validation :

- Any changes made to, for example, procedures, processes and methods, should be managed through the change-control procedure. The extent of validation or revalidation as a result of such a change should be determined based on principles of risk management.

- Where appropriate, periodic revalidation may be performed.





<u>Changes that require re-validation :</u>

*Changes in the manufacturing process (e.g. mixing times, drying temperatures).

*Changes in the equipment (e.g. addition of automatic detection systems).

*Transfer of processes to another site.

*Unexpected changes (e.g. those observed during self-inspection or during routine analysis of process trend data).

Equipment Qualification & Validation



Reference:

* TRS 1019 Annex 3 GMP Guideline on Validation.

* Eudralex Volume 4 (EU Guidelines for GMP for Medicinal products for Human & Veterinary Use)

* PICS PI006-03 Validation Master Plan /Installation and Operational Qualification.

*EMA annex 15 Qualification & validation.

Equipment Qualification & Validation



Any Questions?

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Thank you

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Quality Risk management

Prepared by : Dr Nermine Mohamed

Content

1. Introduction
2. Quality Risk management
3. Quality Risk management Tools.



Introduction :

Risk :



*Possibility of injury or loss , a dangerous element or factor.

*The combination of the probability of occurrence of harm (undesired effect) & the severity of that harm.



Introduction :

Hazard :

*The potential source of harm, things that Present the risk.





Introduction :

Hazard + Exposure = Risk

Hazard	Risk
	Hazard + Exposure



Hints



*All management is Risk management.

*Risk Based thinking is everybody business & not just the responsibility of management.

*Risk based Thinking must become an integral part of organizational culture.



Quality Risk management

A systematic process for the assessment , control , communication & review of risks to the quality of the product or service , process.

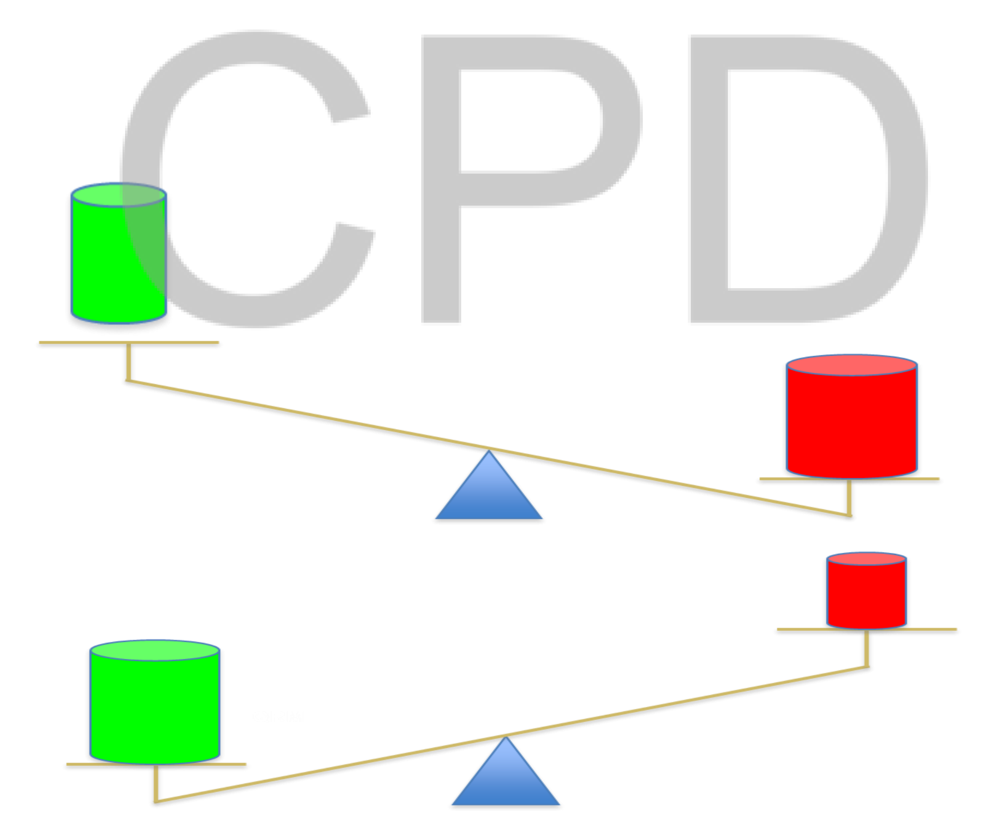




Quality Risk Management

Insufficient QRM

Sufficient QRM



Deviation,
CAPA , OOS,
Change control

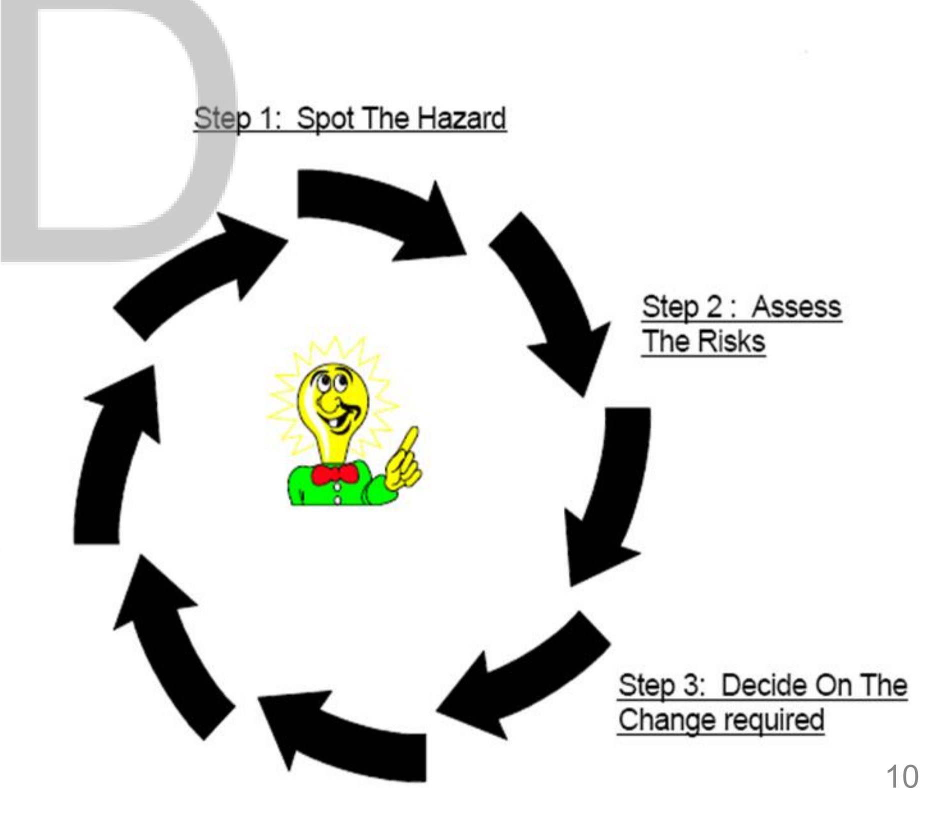
Paper ,
Unproductive
Work waste of
resource



QRM

QRM is a continuous process

*The quality risk management system should ensure that the evaluation of the risk to quality is based on scientific knowledge and experience with the process.





Typical Quality Risk Management process:

Initiate
Quality Risk Management Process

Risk Assessment
Risk Identification
Risk Analysis
Risk Evaluation

Unacceptable

Risk Control
Risk Reduction
Risk Acceptance

Output / Result of the
Quality Risk Management Process

Risk Review
Risk Events

Risk Communication

Risk management tools



1-RA Definition :



A systematic Process for organizing information to support a risk decision to be made within a risk management process. It consists of the identification of the hazard & the analysis and evaluation of the risk associated with exposure to those hazards.

1. Risk assessment

Risk identification → What might go wrong? Systematic use of information to **identify hazards** referring to the risk question or problem (historical data, theoretical analysis, informed opinions).

Risk analysis → What is the likelihood (probability) it will go wrong and how bad can it get? Estimation of the risk associated with the identified hazards. A qualitative /quantitative process of linking the likelihood of **occurrence** of the hazard and **severity** of harm. Consider **detectability**.

Risk evaluation → Compare the identified and analyzed risk against a given **risk criteria** (Risk Rank Table to obtain a Risk Priority Number or RPN).



Three questions are often useful for the three steps:

1-What might go wrong? Risk Identification

2- What is the likelihood (probability) go wrong ? Risk Analysis

3- what is severity (consequence) ? Risk Analysis

*compares the identified and analyzed risk against given risk criteria. Risk Evaluation



Risk Evaluation

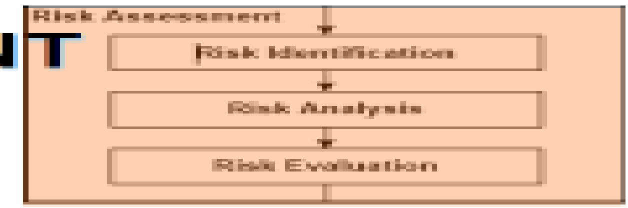
*quantitative estimate of risk (a numerical probability is used).

* qualitative description of a range of risk such as “high”, “medium”, or “low.



Risk Evaluation :

QUALITY RISK ASSESSMENT



Example of Risk table – Acceptance Criteria

probability \ severity	Low Severity	Medium Severity	High Severity
Frequent	Unacceptable	Intolerable	Intolerable
Probable	Unacceptable	Unacceptable	Intolerable
Occasional	Acceptable	Unacceptable	Unacceptable
Remote	Acceptable	Acceptable	Unacceptable

The criteria are arbitrary and only for illustrative purposes

- (green) No reduction or new controls are required
- (yellow) The risk must be reduced or controlled to an acceptable level
- (red) Eliminate the hazard



Probability

P Probability of occurrence Levels for the negative events	
High	The negative event is likely to occur
Medium	The negative event may occur
Low	The negative event is unlikely to occur
Remote	The negative event is very or extremely unlikely to occur

Severity

S	Severity levels for the effects of the negative event
Critical	The effects are severe ➢Very significant GMP/MA non compliance ➢Potential patient injury
Moderate	The effects are moderately severe ➢Significant GMP/MA non compliance ➢Potential patient impact
Minor	The effects are not severe ➢Minor GMP/MA non compliance ➢No patient impact

Detectability

	D Detectability detect control ratings
High	The control will likely detect the negative event or its effects
Medium	The control may detect the negative event or its effects
Low	It is not likely that control will detect the negative event or its effects
Zero	No detection control in place



Assessment Category: (Quantitative)

Assessment - category	1	2	3	4	5
Probability **P**	Low				High
Severity **S**	Slight				Grave
Detectability **D**	High				Low



Risk Priority Number (RPN):

Risk = Probability x Severity
Risk = (P x S)
Risk priority number = Probability x Severity x Detectability
Risk priority Number = P×S×D

Risk and detectability correlation

Risk= Probability X Severity

R=P X S

- Low detectability
- High risk

- High detectability
- Low risk



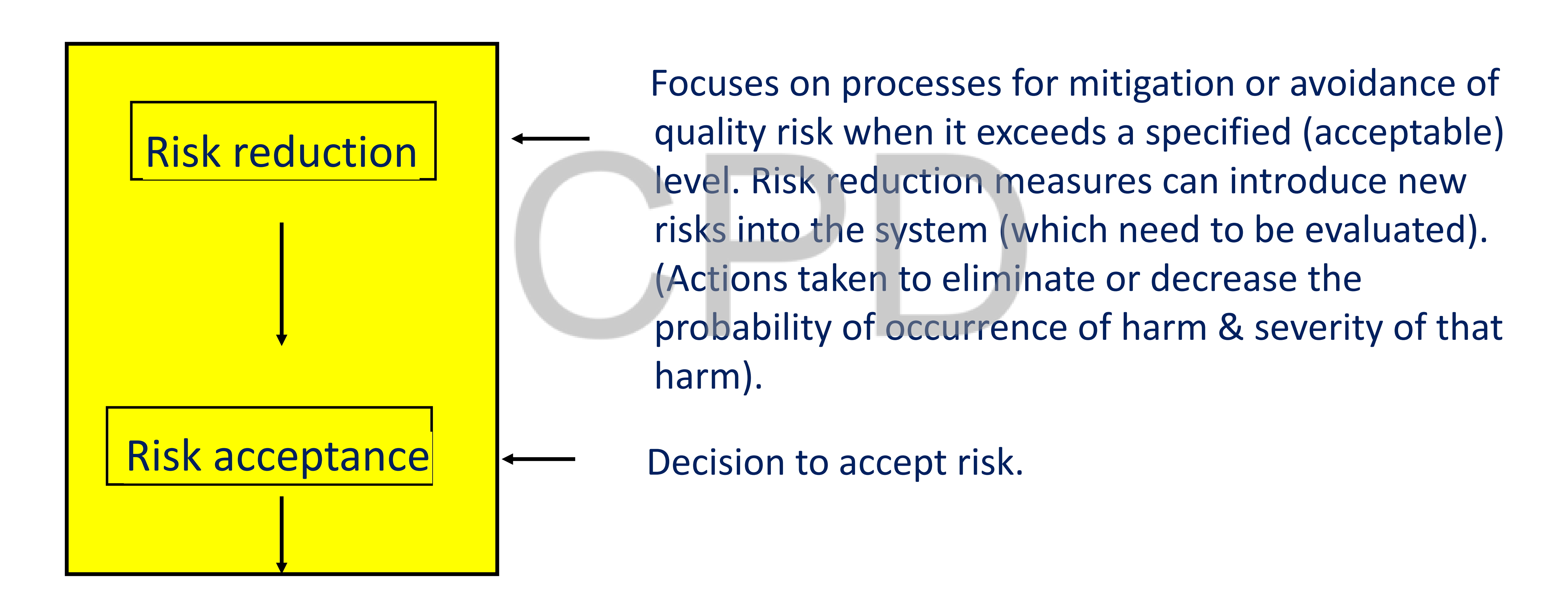
Continue QRM Process



2- Risk Control :

Actions implementing Risk management decisions.

2. Risk control: decision making to reduce and/or accept risks.





Risk reduction

*Risk control includes decision making to reduce and/or accept risks.

*The purpose of risk control is to reduce the risk to an acceptable level.

*The amount of effort used for risk control should be proportional to the significance of the risk.

*Decision makers might use different processes, including benefit-cost analysis, for understanding the optimal level of risk control.



Example Risk Register (non – quantitative)

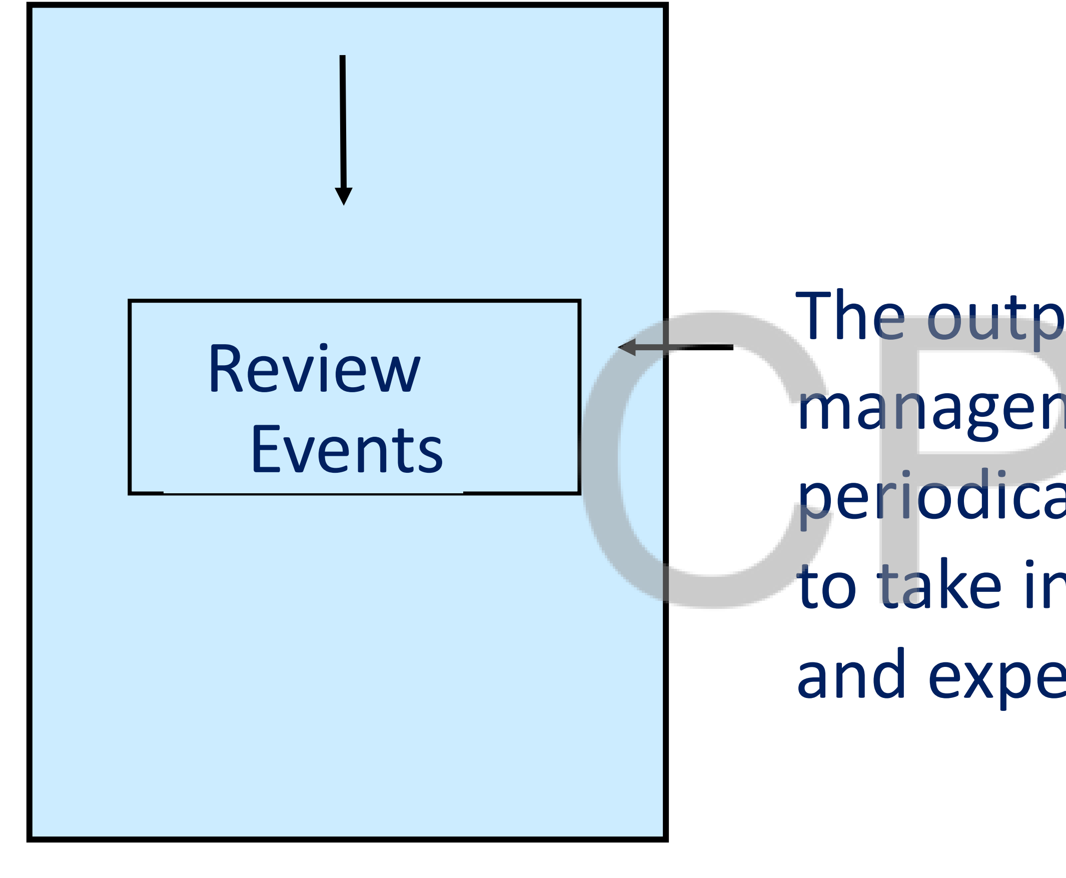
Project name:

Project manager:

Date:

Risk	Probability	Impact	Exposure	Mitigation	contingency
Supplier does not commit to the delivery time of the raw material	medium	high	high	-Review of the delivery time of the supplier. -Contact supplier to make piriorization to raw material.	High priority raw material will be delivered first.

3. Risk review



The output/results of the risk management process should be periodically monitored and reviewed to take into account new knowledge and experience.



4-Risk Communication:

* The sharing of information about risk management between the decision maker and all key stakeholders (within the company, industry and authority, regulators and industry, industry and patients).

*The output / result of the QRM process should be communicated and documented.



Activity

Work Group







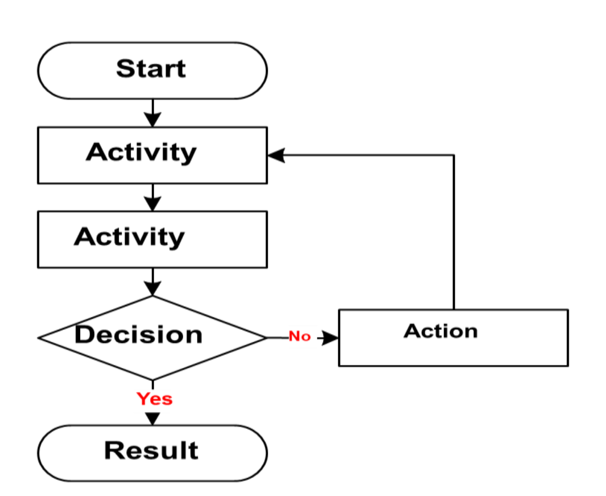




Risk management Tools:

1-Some of the simple techniques that are commonly used to structure risk management by organizing data and facilitating decision-making are:

a-Flowchart.



b-Check Sheets.

Common Questions for Investigating an Out-of-Control Process

❐ Yes ❐ No Are there differences in the measurement accuracy of instruments/methods used?

❐ Yes ❐ No Are there differences in the methods used by different personnel?

❐ Yes ❐ No Is the process affected by the environment, e.g., temperature, humidity?

❐ Yes ❐ No Has there been a significant change in the environment?

❐ Yes ❐ No Is the process affected by predictable conditions? Example: tool wear.

❐ Yes ❐ No Were any untrained personnel involved in the process at the time?

❐ Yes ❐ No Has there been a change in the source for input to the process? Example: raw materials, information.

❐ Yes ❐ No Is the process affected by employee fatigue?

❐ Yes ❐ No Has there been a change in policies

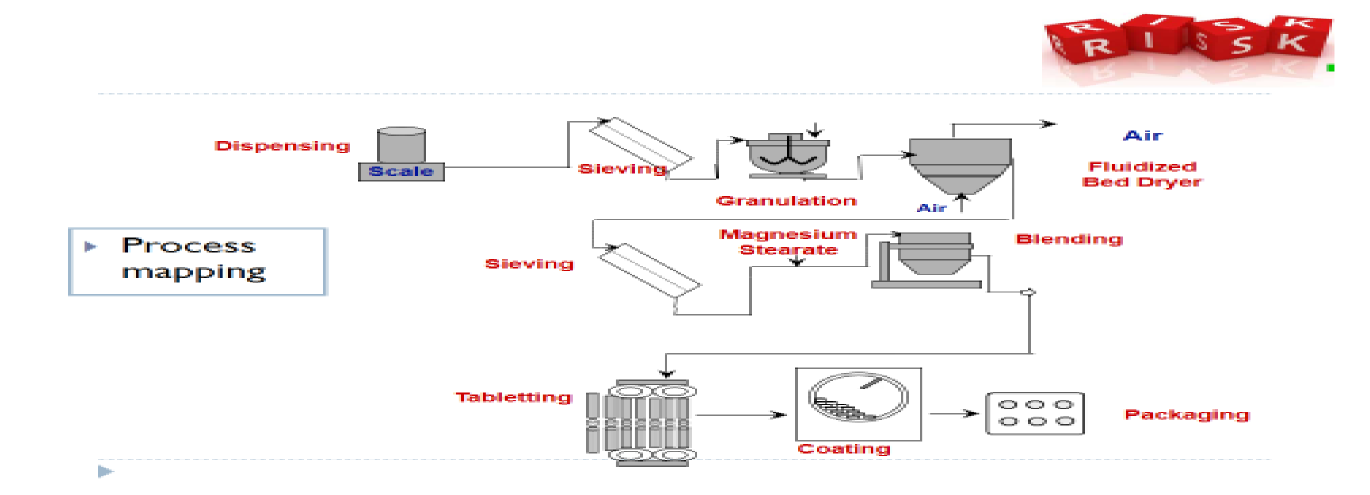


Risk management Tools:

1-Some of the simple techniques that are commonly used to structure risk management by organizing data and facilitating decision-making are:

c-Process mapping

d-Cause & Effect Diagram





Material

Measures

Manpower

Supplier

Input

Process

Output

Customer

Methods

Machine

Environment



Example :

1-Material : Low grade.
2- Measures : trend , monitoring , ……
3- Manpower : training , Skills,……
4- Supplier : unqualified.
5- Methods : Not validated.
6- Machine : not qualified , old,…..
7- Environment : Area condition.
8- Customer : does not give feed back on product.



Cause & Effect Diagram For Tablet Hardness

Coating
Spray Rate
Pan Speed
Gun Distance
Temperature
Atomizing Air Pressure

Drying
Temperature
Redrying
Time
Milling
Temp
RH
Air Flow
Shock Cycle

Milling
Screen Size
Porosity
Mill Speed

Analytical
Other
Sampling
Method

Tablet Hardness

Plant Factors
Operator
Temp/RH
Operator
Training

Compressing
Precompressing
Main Compressing
Feeder Speed
Press Speed
Punch Penetration
Depth
Tooling
Feed
Frame

Granulation
Water
Binder
Temp
Spray Rate
Spray Pattern
P.S.
Scrape Down
Chopper Speed
Mixer Speed
Endpoint
Power
Time

Raw Materials
Drug Substance
Age
P.S.
Process Conditions
LOD
HPMC
Methoxyl
Hydroxyl
P.S.
LOD
Other
Syloid
Lactose
Coating

CPD



FISHBONE DIAGRAM (ISHIGAWA DIAGRAM)



FISHBONE DIAGRAM (ISHIGAWA DIAGRAM)

Simple Fishbone Diagram

Bioburden Levels Out of Specifications

- **People**: Training, Skills, Shift pattern
- **Methods**: Manual, Automated, Human factors
- **Machines**: Maintenance, Validation, Capability
- **Materials**: New supplier, Storage, Supply chain
- **Measurement**: Calibration, Training
- **Environment**: Cleaning materials, Cleaning schedules, Training

→ **Failure**



Risk management Tools:

2-Failure Mode & Effects Analysis (FMEA):

*FMEA is a powerful tool for summarizing the important modes of failure, factors causing these failures and the likely effects of these failures.

*FMEA relies on product and process understanding.

*FMEA methodically breaks down the analysis of complex processes into manageable steps.



FMEA :

Step	potential failure	Cause	Controls	S	P	D	RPN	Measures taken	S	P	D	RPN
Manufacturing (as General)												



FMEA Example:

Step	Potential failure	Cause	Controls	S	P	D	RPN	Measures taken	S	P	D	RPN
sampling of raw material	Escape of dust "generated during sampling process" from sampling area and ingress to adjacent area. (contamination	doors opens directly to the adjacent areas No pressure differential between sampling room and adjacent area Improper personnel flow or /gowning /de-gowning procedure	-Room is separated from WH through two airlocks for personal flow -sampling room is negative to adjacent areas with diff. pressure 10- 20 Pa -Sampling processes are performed under fixed extraction booths with HEPA filter (H14) and curtains extraction of any generated dust and control air laminarity, containment and sampler protection.	3	3	1	9	Routine Verification of Differential pressure across: AHU filtration stages, Rooms of sampling area Filters of LAF booth Filters of pass box Current controls cover the risk	3	1	1	3



Process step	Parameter	Possible hazard, risk concern	P	S	D	RPN	Risk mitigation
MILLING	• Sieve size	• Too large mesh size will lead to loss of uniformity in particle size distribution and formation of lumps of ingredients especially XXXX thereby compromising powder flow characteristics and subsequently tablet compression and uniformity of mass and content. • Too small mesh size will lead to generation of too much fines in the powder thereby affecting powder flow through the hopper, subsequently affecting tablet mass and content uniformity, hardness. In addition, this will cause tablets capping.	2	5	2	20	• Use of optimum screen size of 1.5mm (round mesh) • Impacts on powder and product characteristics have been evaluated and optimized during process optimization studies and will also be evaluated in the later stages of the process of this process validation
BLENDING	• Blending Time	• Too short blending time will lead to inadequate mixing resulting to failure in uniformity of content, poor powder flow characteristics, affecting smooth run of the tablet press ultimately affecting tablet quality in terms of uniformity of mass, hardness, friability and disintegration. • Too long blending time lead to segregation with similar effects as inadequate mixing above.	2	5	5	50	• Use of predetermined optimum blending time
	• Blending Speed	• Too high speed would disrupt particle size distribution profile of the final blend through generation of excess fines, subsequently affecting powder flow characteristics and by extension tablet uniformity of mass, hardness, friability and tablet physical attributes. • Too slow speed would result to inadequate mixing of the powder leading to the effects mentioned above.	2	5	5	50	• Optimum blending speed. • Preventive maintenance and machine qualification.
	• Blender fill level	• Low fill level (less than 50 % capacity) may lead to trajectory and percolative segregation of the powder mix. • High fill level (more than 80 %) capacity will lead to improper distribution of lubricants due to lack of space for the powder to turn and mix freely.	2	5	1	10	• Uses of determined optimum fill level of 65 %± 15 % fill level i.e. 50-80 %
LUBRICATION	• Blending time	• Improper lubrication can cause poor powder flow leading to variation of mass, poor tablet ejection and	2	5	5	50	• Uses of optimum blending time, Blender fill level and the blend content



Risk management Tools:

-FMEA method is the most commonly practiced form of risk assessment and risk control.

FMEA is a preventative method that provides an evaluation of potential failures in terms of:

- severity of the failure (S)
- probability of likelihood (occurrence) of the failure (P or O).
- probability of detecting the failure (D).



Risk management Tools:

3- Failure Mode, Effects and Criticality Analysis (FMECA)

*FMEA might be extended to incorporate an investigation of the degree of severity of the consequences, their respective probabilities of occurrence, and their detectability, thereby becoming a FMECA.

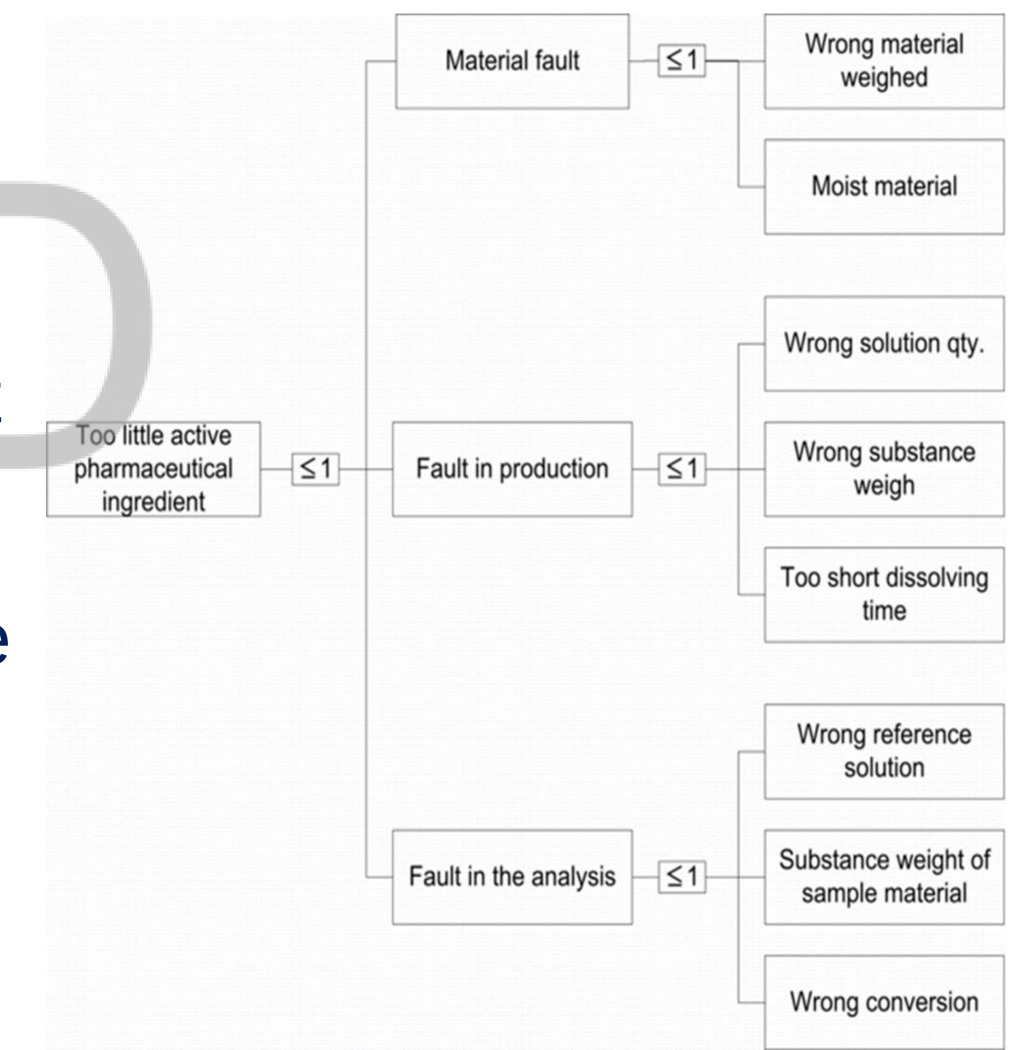
*In order for such an analysis to be performed, FMECA can identify places where additional preventive actions might be appropriate to minimize risks. the product or process specifications should be established.



Risk management Tools:

4-Fault Tree Analysis(FTA):

*It is used to establish a pathway to the root cause of the failure.
*It is used to investigate complaints or deviations in order to fully understand the root cause.





Risk management Tools:

5-Hazard Analysis and Critical Control Points (HACCP):

*it might be used to identify and manage risks associated with physical, chemical and biological hazards.



Risk management Tools:

6-Hazard Operability Analysis (HAZOP) :

* It is based on a theory that assumes that risk events are caused by deviations from the design or operating intentions.

Deviation	Causes	Consequences	Safeguards	Recommend
High temperature in blender	Steam heating control malfunction	● Feed material #1 reaches decomposition temperature ● Violent reaction with toxic gas generation ● Personnel exposure/ injury ● Equipment damage	● Diverse high temp. interlock on blender ● Blender vented	● Test interlock on quarterly basis ● Add steam heating control to monthly PM



Risk management Tools:

7-Preliminary Hazard Analysis(PHA) :

*Is a tool of analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards.

*Is most commonly used early in the development of a project when there is little information on design details or operating procedures, thus it will often be a precursor to further studies.

Hazards Arising From Product Design				
Hazard	Investigation/ Controls	Sev	Freq	Imp (SxF)

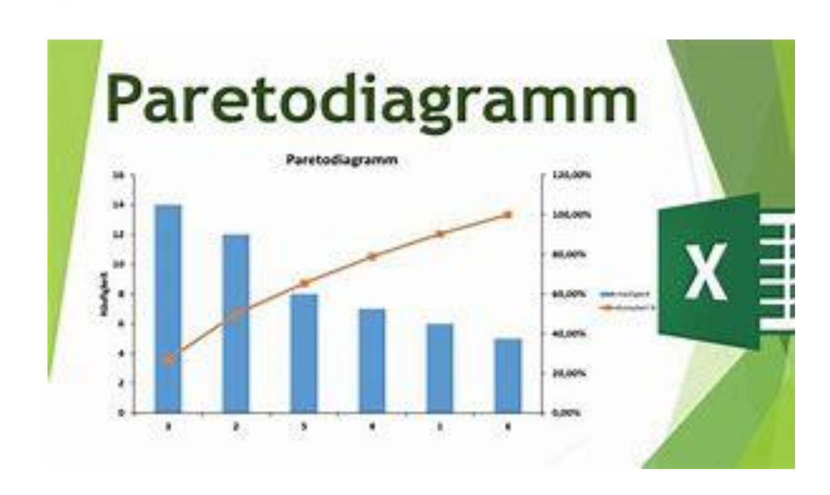


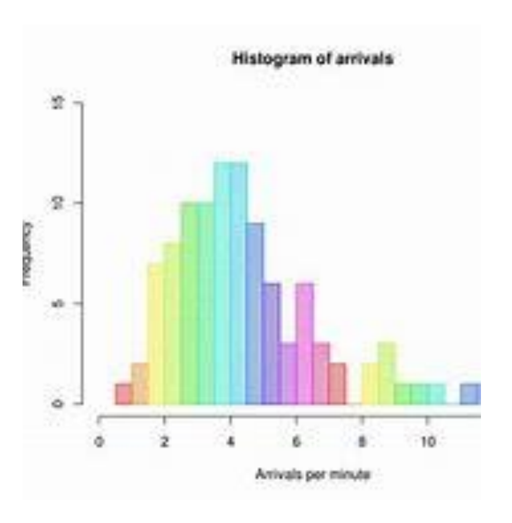
Risk management Tools:

8-Supporting statistical tools :

*control charts Pareto charts histograms

Upper Control Limit
Average
Lower Control Limit
Variable
Time







Risk management Tools:

-Which method of risk management has to be used?

-There is no “one-size fits all” method ,no single tool or combination of tools is applicable
to every situation in which QRM procedure is used.





References

- ICH Q9 Quality Risk management.

- TRS 957 annex 3 (WHO good manufacturing practices for pharmaceutical products containing hazardous substances).

- ISO 31010/2019.

- TRS 981 annex 2 (Quality Risk assessment)



Any Questions?







Thank you

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Temperature mapping of storage areas

Presented by:
Dr. Mohamed Salah
GMP Lead Inspector & Trainer
Drug factory inspection administration

Content

1. Introduction



- Temperature mapping procedure includes any cold room, freezer rooms or other temperature-controlled store.(staging areas…)
- Depending upon the routine monitoring strategy, subsequent mapping exercises may also be required periodically – for example, every three years –in order to demonstrate continuing compliance.

1. Introduction



The temperature mapping procedures should:

■■ demonstrate the air temperature profile throughout the storage area, when empty and in a normal loaded condition;

■■ define zones which should not be used for storage of TTSPPs (for example areas in close proximity to cooling coils, cold air streams or heat sources); and

■■ if required, demonstrate the time taken for temperatures to exceed

the designated limits in the event of a power failure.



In addition mapping should be carried out whenever significant modifications are made to the store.

Examples include changes in the pattern of use that may increase loading or affect air circulation, or changes to the refrigeration equipment, such as an alteration to the set point.

Finally re-mapping may be justified whenever an analysis of temperature and/or humidity monitoring records shows unexplained variability outside normal operating limits.



- A temperature mapping exercise is required for any space allocated for the storage and handling of products with a specified labelled storage temperature.
- This includes freezer rooms, cold rooms, temperature-controlled storage areas, quarantine areas and receiving and loading bays. It may also include laboratories.
- The permitted temperature ranges in these areas will vary – for example: -25°C to -10°C, **2°C to 8°C, 15°C to 25°C**, etc.
- Temperature mapping may also need to be carried out in spaces without active temperature control.



Mapping may also be used to identify zones where remedial action is needed; for example by altering existing air distribution to eliminate hot and cold spots, or by retro-fitting new air distribution equipment



➢A mapping study establishes the temperature distribution within the zone being mapped and it locates hot and cold spots.

A temperature mapping exercise involves a four stage process, as follows:

a. Prepare a mapping protocol.

b. Carry out the mapping exercise.

c. Prepare a mapping report.

d. Implement the recommendations by carrying out the remedial and other actions identified in the mapping report.

➢ A follow-up mapping exercise may then be needed to verify the effectiveness of the remedial actions.

The mapping protocol



- A detailed and comprehensive protocol should be prepared, reviewed and approved before the mapping exercise begins.
- A well-designed protocol will help ensure that the mapping study is correctly carried out. With suitable adjustments or options to cover the full range of temperature regimes, a standard protocol can be used to map any storage area in the facility.

The mapping protocol (cont.)



➢ The mapping protocol should contain the following sections:

1. Approval page and change control history.
2. Acronyms and glossary.
3. Description and rationale.
4. Scope.
5. Objectives.
6. Methodology
7. Mapping report template.
8. Annexes as needed, including templates for the mapping report .



2.2.1 Approval page and change control history:



Include a standard template for recording approvals and changes to the document. The following is an example:

Approvals	Name	Date	Signature
Authorized by:			
Reviewed by:			
Revised by:			
Original author:			





No	Date	Description of change	Reason for change
1		Original	
2			
3			
4			
5			

- If the protocol has been prepared by a qualified third-party, it should be authorized by the responsible person within the commissioning organization.

Acronyms and glossary:



- Define the acronyms and technical terms used in the protocol



Description and rationale



- Describe the installation to be mapped and outline the reasons for carrying out the exercise.



Scope:



- Clearly define the scope (F.P warehouse, R.M WH…) and purpose of the mapping study.
- The fundamental purpose is to identify temperature deviations affecting the chosen storage area(s) at the time the study is being conducted, so that remedial action can be taken.
- Preferably, at least two temperature mapping studies should be carried out in each area. In order to observe the effect of seasonal variation, one should be carried out during the warmest season and one during the coldest season.
- This will establish whether the mapped area is able to maintain stable temperatures throughout the year.

Objectives:



❖ Clearly define the detailed objectives of the study, as follows:

- *Mapping temperature variations within the selected storage areas. Typically these areas include freezer rooms, cold rooms, warehouses, loading bays and other areas in which temperature sensitive products are stored, or are temporarily held when in transit.*
- Measuring temperature variations at each location within the chose area, by day of the week, and time of day.
- Documenting high and low temperature fluctuations

Objectives: (cont.)



- Identifying potential airflow issues that may be the cause of temperature variations.
- Recommending where TTSPS can safely be stored in the mapped area. These recommendations should take account of any temperature deviations identified during the study as well as the approved temperature range(s) for the products being stored in the area.
- Identifying the best places to locate temperature sensors, for routine monitoring. If a monitoring is already installed, identify the best places to re-locate temperature sensors (if necessary).

Methodology



❖ The following steps outline the methodology for conducting a temperature mapping study.

➢ STEP 1 – select EDLMs: .

- Choose a device that has sufficient memory for the intended duration of the study and the selected recording interval.
- all loggers must have a 3-point calibration completed and valid (within the current year), and have an error of no more than ± 0.5°C at each calibration point.

Associated materials and equipment



➢A mapping operation requires a sufficient number of Electronic Data Logging Monitors (EDLMs) to ensure that the temperature distribution in the space to be mapped is adequately characterized. In addition, suitable computer equipment and software is needed to store and analyse the data.

Associated materials and equipment



➢ **<u>The selected EDLMs must:</u>**

❑ Be technically suitable for the specific mapping task and for the intended operating environment;

❑ Provide a reliable and continuous reliable record of time-temperature data;

❑ Have an appropriate temperature range so that all anticipated temperature extremes can be recorded (e.g. from -30°C to +60°C)

❑ Have a user-programmable data sampling period, with time intervals ranging from one minute to 15 minutes or more and sufficient memory for the intended length of the study and the chosen recording interval;

❑ Have 3-point calibration certificate with a guaranteed error of no more than ± 0.5°C at each calibration point.

❑ Allow the recorded time-temperature data to be downloaded to a computer system for subsequent analysis;

❑ Have data storage software that complies with applicable regulatory requirements (21 CFR part 11)

Methodology (cont.)
STEP 1 – select EDLMs:



- Valid calibration certificates for each of the data loggers used in the study must be included in the mapping report.

Calibration temperature points used for the calibration of EDLMs should cover the required temperature range for each of the areas being studied. In general there should be one calibration point below the low end of the range, one calibration point in the middle of the range, and one calibration point above the high end of the range.

- To ensure consistency, use only one type of device per mapping study.

Methodology (cont.)



➢ <u>STEP 2 – designate the mapping team:</u>

- Identify and list the team members.
- Record their signatures and initials so that signed records can be traced back to the person who prepared the document.
- . Ensure that all team members receive the training needed to perform their assigned tasks.

Methodology (cont.)



➢ STEP 3 – survey the site:

- Conduct a site survey of the area(s) to be mapped.

❖ The following information is required for each thermally separate area being mapped:

- Length, width and height dimensions.
- Drawing of each area, showing elements, such as shelving or pallet racking, that may have an effect on the even heating or cooling of the space and which may have an effect on its temperature stability. The shelving or pallet racking will be used to place the EDLMs, so it is important to record these components accurately.

Methodology (cont.)

STEP 3 – survey the site: (cont.)



- The location of heating and cooling components, including air distribution outlets and/or ceiling fans.
- The location of existing temperature recording sensors and temperature controlling sensors.

Methodology (cont.)



- STEP 4 – establish acceptance criteria:

- the protocol should define the required acceptance criteria, based on the type of TTSPs being stored, clearly stating the temperature limits that are allowable within the area to be mapped – for example: +2°C to +8°C or +15°C to +25°C.

Methodology (cont.)



➢ STEP 5 – determine EDLM locations:

▪ Use the site survey to mark the required locations of the EDLMs.

❖ The following guidelines will help determine the number and location of the EDLMs required:

▪ Length and width: EDLMs should be arranged in a grid fashion along the width and length of the area so that the area is reasonably covered, with EDML locations every 5-10 meters.

▪ The chosen sensor grid should take account of:

▪ The layout of the area.

▪ The degree to which shelving and products may affect airflow.

▪ Where products are placed. The positions of EDLMs should coincide with locations where TTSPs are actually stored or planned to be stored. For example, it may be unnecessary to fit EDLMs in areas such as the upper part of high loading bays.

Methodology (cont.)
STEP 5 – determine EDLM locations: (cont.)



❖ <u>Height: At each point on the grid, arrange EDLMs vertically as follows:</u>

- If the ceiling height is 3.6 meters or less, position EDLMs directly above one another at high , medium, and low level (e.g. one EDLM at floor level, 1.2 meters and one EDLM at 3.0 meters.
- If the ceiling height is greater than 3.6 meters, arrange EDLMs in vertical arrays at the bottom, middle (Multiple) and top of the space. For instance, for a storage area six meters in height, three EDMLs should be positioned in each grid location heights of 1.8 meters, 3.6 meters and 5.4 meters.

Methodology (cont.)
STEP 5 – determine EDLM locations: (cont.)



- Give each logger location a unique ID. It may be helpful to use a generic floor plan or diagram to decide where each logger should be positioned.

Methodology (cont.)

STEP 5 – determine EDLM locations: (cont.)



DL015
DL011
DL007
DL014
DL010
DL006
DL013
DL009
DL005
DL01
DL008
DL004

Methodology (cont.)

STEP 5 – determine EDLM locations: (cont.)



Typical location of data loggers in a walk-in cold room

DL01
DL02
DL03
DL04
DL05
DL06
DL07
DL08
DL09
DL10
DL11
DL12
DL13
DL14
DL15
DL16
Controlling RTD

Additional sensors:
DL17, 18: Directly in front of evaporator grilles
DL19, 20: Near refrigerator unit condensers to monitor heat build-up

RTD: Recording Temperature Device

Methodology (cont.)



➢ STEP 6 – record EDLM and thermostat locations:

- Record the EDLM locations on a temperature data logger location table.
- Also record the location identification .

Methodology (cont.)



➢ STEP 7 – label and program the EDLMs:

- Label each EDLM with a unique ID, taken from the temperature data logger location table.
- Enter the manufacturer's serial number on the temperature data logger location table.
- Recording the serial number ensures that the device can be traced to its calibration certificate.
- Program each device, ensuring that the recording interval is the same – typically this should be set between 1 and 15 minutes.
- Set the same start time for all units.
- otherwise the downloaded readings from the individual devices cannot be time-correlated.

Methodology (cont.)



Test data sheets

The following sections show examples of the type of data collection forms used in a mapping exercise.

A1.1 **Test data sheet: temperature data logger locations**

Data logger ID number	Data logger serial number	ID number on schema	Mounting height (metres)	Description/comments
DL-001		1	0.3	
DL-002		2	2.8	
DL-003		3	5.4	
DL-004		4	0.3	
DL-005		5	2.8	
DL-006		6	5.4	
DL-007		7	0.3	
DL-008		8	2.8	
DL-009		9	5.4	
DL-010		10	0.3	
DL-011		11	2.8	
DL-012		12	5.4	
DL-013		13	0.3	
DL-014		14	2.8	
DL-015		15	5.4	
DL-016		16	0.3	
DL-017		17	2.8	
DL-018		18	5.4	
DL-019		19	0.3	

Methodology (cont.)



Thermostat information	
Location	Set point
Near entrance door #1	20 °C
Near loading dock #4	20 °C

Methodology (cont.)



➢ STEP 8 – fix EDLMs in position:

- Fix the EDLMs in position.
- Make sure that each one is placed exactly as shown on the temperature data logger location table and drawing.
- Position and fasten the devices so that they cannot be damaged or displaced during the course of routine store operations.

Methodology (cont.)



➢ STEP 9 – conduct the mapping exercise:

- Typically it should be run for a minimum of seven consecutive days including five working days and two weekend days. for warehouses and other ambient storage areas.

For temperature-controlled equipment which is not critically affected by diurnal or seasonal variations in ambient temperature (e.g. freezer rooms and cold rooms) the mapping study should be run for between 24 and 72 hours, or more if justified.

Methodology (cont.)



If the room is fitted with duplicate refrigeration units – with or without automatic changeover – it is essential to map temperatures over a period that includes the operation of both units running separately; preferably for a similar time period. The temperature distribution in the room may vary depending upon which system is running.

- At the end of the study, collect the EDLMs and double-check their serial numbers and locations against the installation notes.

Methodology (cont.)



➢ <u>STEP 10 – download and consolidate the data:</u>

- Download the EDLM readings and consolidate the data for the study analysis.

Methodology (cont.)



Test data sheet: temperature distribution

Data logger ID number	Minimum temp. recorded (°C)	Maximum temp. recorded (°C)	Mean temp. (°C)	Within range?		Inspected by	Date
				Yes	No		
DL-001	18.6	22.4	20.5	☒	☐	JB	
DL-002				☐	☐		
DL-003				☐	☐		
DL-004				☐	☐		
DL-005				☐	☐		
DL-006				☐	☐		
DL-007				☐	☐		
DL-008				☐	☐		
DL-009				☐	☐		
DL-010				☐	☐		
DL-011				☐	☐		
DL-012				☐	☐		
DL-013				☐	☐		
DL-014				☐	☐		
DL-015				☐	☐		
DL-016				☐	☐		
DL-017				☐	☐		
DL-018				☐	☐		
DL-019				☐	☐		
DL-020				☐	☐		
DL-021				☐	☐		
DL-022				☐	☐		
DL-023				☐	☐		

Mapping report template



- The protocol should contain a template for the mapping report.

❖ This should include the sections listed below:

a. Introduction: a description of the objectives of the mapping study.

b. Summary: a summary and discussion of the results organized in the sequence set out in the mapping protocol, including a summary of deviations (if any).

c. Conclusions and recommendations: a general conclusion for all verifications and observations indicating the acceptability of the equipment for operation. Recommendations and remarks can be incorporated as well.

Mapping report template (cont.)



d. Report annexes: The report annexes should contain the following:

- The site survey, showing EDLM locations.
- The raw data, presented using the appropriate test data sheet format.
- Spreadsheet data and related temperature graphs for every EDLM used in the mapping exercise.
- Key documents and notes prepared during the mapping exercise, together with any other supporting material.
- Deviation reports, including Corrective and Preventive Actions (CAPA) forms, if required.
- Calibration certificates for all EDLMs used.

Analyzing the data and preparing the mapping report



❖ The following sub-sections outline the data analysis process that precedes the writing of the report.

-Preliminary analysis.

- Minimum and maximum temperatures and hot and cold spots.

- Mean temperatures.

- Interpreting the results and making recommendations.

- Report auditing.

Preliminary analysis.



- Analyze the overall temperature stability of the study area and identify the variations that occur.
- Compare the measured temperatures against the acceptance criteria.

❖ The analysis of the overall temperature stability should consider factors such as:

1- The ability of the environmental control systems to maintain temperatures within the acceptance criteria limits (if any).

2- The overall temperature stability of the area being monitored, and the range in fluctuations it experiences over the study period.

Preliminary analysis. (cont.)



❖ The analysis of temperature variations should consider factors such as:

- Variations experienced by individual EDLMs.
- Temperature variations along vertical and horizontal planes, depending on the size of the area, and distribution of EDLMs.
- Temperature variations in locations close to heating and cooling components, as compared to those farthest away from these units.

Minimum and maximum temperatures and hot and cold spots



- A mapping study measures temperature fluctuations.
- From these data, the analyst can identify the minimum and maximum temperatures that occur in the mapped area during the study period.



Minimum and maximum temperatures and hot and cold spots (cont.)



- A cold spot refers to the lowest temperature value(s) recorded in the space over the study period, but with these lowest temperature value(s) remaining within the specified temperature range (e.g. cold spots identified between +15°C to +17.5°C in a room with a specified temperature range +15°C to +25°C).
- A hot spot refers to the highest temperature value(s) recorded in the studied area over the study period, but with these highest temperature value(s) remaining within the specified temperature range (e.g. hot spots identified between +23°C to +25°C in a room with a specified temperature range +15°C to +25°C).



Minimum and maximum temperatures and hot and cold spots (cont.)



Use of mean temperatures

30
25
20
15
10

Temperature (C)

Time

Temperature 1 (recorded)
Temperature 1 (mean)
Temperature 2 (recorded)
Temperature 2 (mean)

Interpreting the results and making recommendations



➢ how to interpret the results, and how to use these results to support the report's recommendations:

- Document the internal temperature variations observed within the space, taking account of the EDLM reading errors specified by the device manufacturer.
- Use the data analysis to assess the overall temperature stability of the mapped space in relation to the stated acceptance criteria (if any).
- Assess the overall thermal stability of the space during the study period with specific reference to the high and low temperatures experienced.

Interpreting the results and making recommendations (cont.)



- List the factors that explain the observed temperature variations. For example, the location of the heating and cooling components and doors.
- Assess consistent and inconsistent temperature variations, and fluctuations, within the space in terms of their potential impact on product storage.
- Based on the observed temperature fluctuations of mapped locations within the space, make recommendations about the optimum storage locations for highly sensitive products, and those that are less sensitive.
- Based on the observed temperature fluctuations of mapped locations within the space, make recommendations on the optimum location of the temperature sensor(s) used for routine temperature monitoring and the control sensors used to activate the heating and cooling systems.

Report approval



- The report content, including data sheets, results, spreadsheets and graphs should be audited and peer-reviewed by a competent independent person.
- The reviewer should confirm, approve and sign the major reported test and verification results and the recommendations arising from these results.
- If the report has been prepared by a qualified third-party, it should be approved by the person who commissioned the study.

Implementing the mapping report recommendations



➢The final outcome and purpose of a mapping exercise is the implementation of the report recommendations. A detailed discussion of implementation is outside the scope of this document, but it could include any of the following outcomes:

- A drawing or diagram showing where TTSPPs can safely be stored in the space that has been mapped. It is possible that there may be some zoning involved. For example, products which are not affected by freezing could be allocated to parts of a cold room where the mapping study has shown some freezing risk.
- Allocation of pallet bays to specific categories of TTSPP on the warehouse management system in order to control where stocks are positioned.
- Re-positioning of temperature monitoring sensors and/or environmental control sensors.
- Adjustment of air outlets to reduce temperature stratification and/or minimize cold and hot spots.
- Upgrading of mechanical systems to improve temperature control and performance.
- A decision to use the space for other purposes because it is unsuitable for storage of TTSPPs.

Challenging the area with Operational Activities

1. By performing these functions and processes, cause and effect relationships can be identified for the thermal mapping study.

2. Activities must simulate the normal processes that would occur for routine operations, such as:

A. Opening internal doors.

B. Opening external doors (receiving dock doors, shipping dock doors).

C. Running of equipment (stretch wrappers, forklifts, conveyors).

Open Door Recovery Test

1. It is recommended to determine the time that the chamber door may remain fully open before the monitoring sensors are no longer within the acceptable range (maximum time allowed).

2. It also give us a picture for the recovery time needed for all monitoring sensors to return within the acceptable range (recovery time).

3. It is recommended to set the data acquisition rate to 1 minute intervals for this test, because of uncertainty in the time that the test may take.

4. Generally, no specific acceptance criteria for this test.

5. For large walk-in cold rooms, vinyl curtains should make the open door time larger and the effect of fluctuation is neglectable.

Power Outage
(Recovery from power failure or power interruption)

1. It is recommended for business continuity and disaster recovery perspective.

2. It measures the time for the room/space remained within the desired temperature range once electrical power was turned off.

3. Although backup power generators are in place, the results of this test provide data to define how quickly materials need to be moved to another location if the backup power systems failed.

4. Doors should be closed during this test.

Power Outage
(Recovery from power failure or power interruption)

6. Once power is restored, the time required to have the area return to desired temperature range is of a big value for operational considerations, recovery from disaster, or after maintenance activity.

7. It is recommended to set the data acquisition rate to 1 minute intervals for this test, because of uncertainty in the time that the test may take.

8. Generally, no specific acceptance criteria for this test.

- ❑ Measurement uncertainty of sensors should be considered upon establishing the alarm limits.

- ❑ Measurement uncertainty calculation and application:

For the low limit

$$DL \geq LIMIT + (GB - U_{st})$$

For the high limit

$$DL \leq LIMIT - (GB - U_{st})$$

Where:

DL = Decision limit
Limit = Action limit
(GB) Guard band = k * U_{system}
k = coverage factor which must be ≥ 2 "corresponds to confidence level ≥ 97.7%"
U_{system} = Calculated measurement uncertainty
U_{st} = Required uncertainty of limits (usually = 0 to indicate no allowable excursion from the alarm value)

- Given that U_{system} = 0.125 °C
- U_{st} = 0 (no tolerance in readings is required)
- Measurement uncertainty calculation and application:

For the low limit

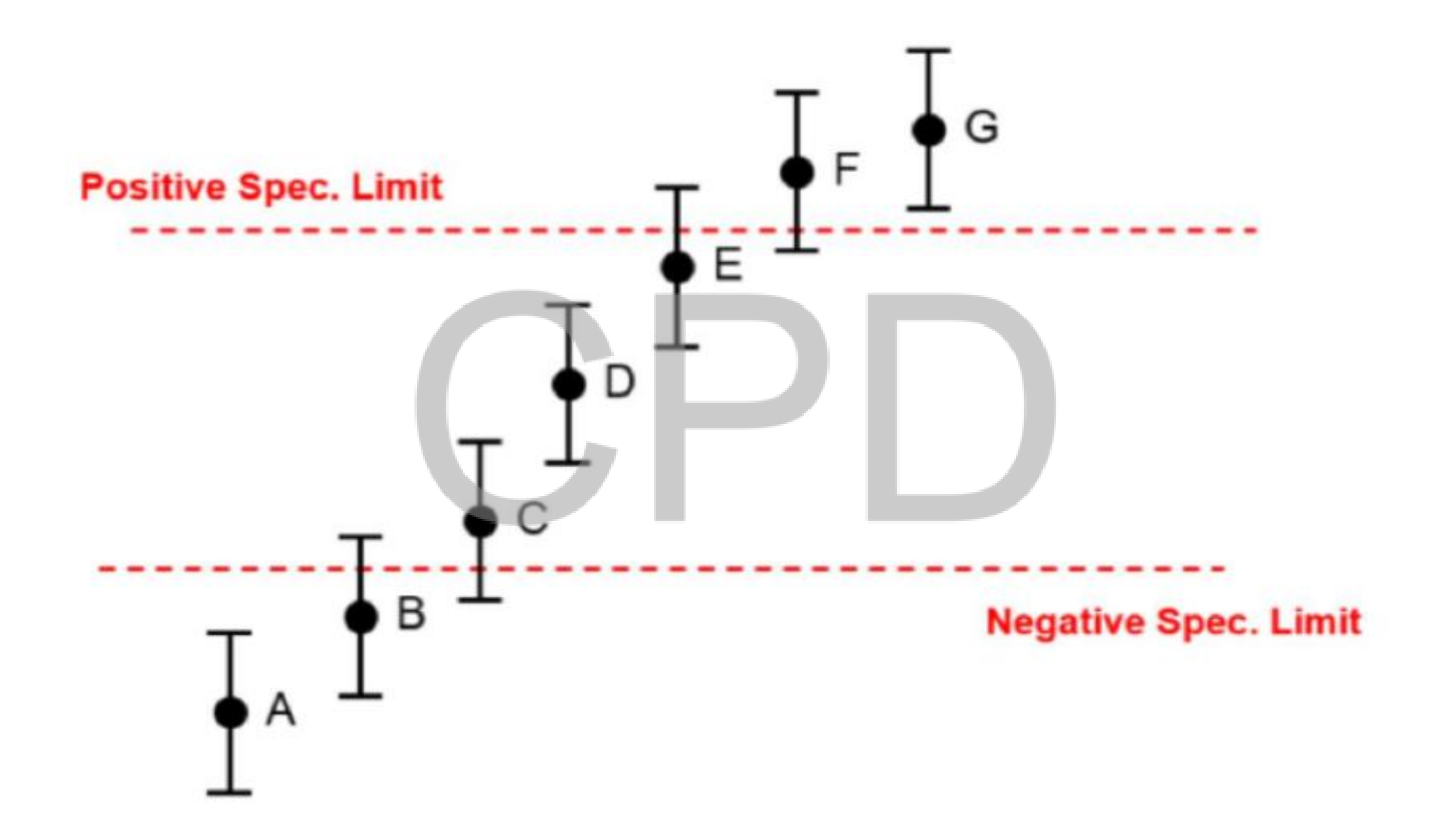
$$DL \geq LIMIT + (GB - U_{st})$$

$$DL_H = 8 - (2*0.125 - 0) = 8 - 0.25 = 7.75°C$$

For the high limit

$$DL \leq LIMIT - (GB - U_{st})$$

$$DL_L = 2 + (2*0.125 - 0) = 2 + 0.25 = 2.25°C$$



Positive Spec. Limit
G
F
E
D
C
B
A
Negative Spec. Limit

- Mean Kinetic Temperature (MKT) is defined as the single calculated temperature at which the total amount of degradation over a particular period is equal to the sum of the individual degradations that would occur at various temperatures.

- MKT integrates the time–temperature history and takes into account the fact that long temperature excursions at slightly elevated temperatures can be just as, or more, impactful than short temperature excursions at elevated temperatures.

- A common storage condition for many pharmaceuticals is "controlled room temperature;" the USP describes "controlled room temperature" as a temperature that includes the typical environment of 20 °C to 25 °C, where excursions are allowed between 15 °C and 30 °C provided that the mean kinetic temperature remains at or below 25 °C.

$$T_K = \frac{\frac{\Delta H}{R}}{-\ln\left(\frac{e^{\left(\frac{-\Delta H}{RT_1}\right)} + e^{\left(\frac{-\Delta H}{RT_2}\right)} + e \ldots + e^{\left(\frac{-\Delta H}{RT_n}\right)}}{n}\right)}$$

T_K = Mean Kinetic Temperature

ΔH = Activation energy contant, typically 83.14472 J mol^{-1}

R = Gas constant, 8.314472 x 10^{-3} J mol^{-1} K^{-1}

T_1-T_n = Temperature in Kelvin (each sample point from 1 to n is used)

n = Number of sample points

e = Natural log base

Application of this formula is more straight forward than it appears. T_1 is the average temperature recorded over the first time period, T_2 is the average temperature recorded over the second time period, etc, to the nth time period.

- Step 1: Convert °C to Kelvin by adding 273.15 to each reading.
- Step 2: Calculate the following for each reading:

Delta H/(Gas Constant x Temperature Reading)

- Step 3: Calculate the sum of all results of Step 2.

This is simple! Simply sum up all values.

- Step 4: Divide the result of Step 3 by the number of readings n.
- Step 5: Calculate natural logarithm of result in Step 4.

Now Denominator is over.

- Step 6: Calculate Numerator.
- The numerator is Delta H divided by Gas Constant.

$$= \Delta H/R = 83.144/0.0083144 = 10,000$$

- Step 7 : Calculate numerator by the denominator (Divide).
- Step 8: Convert Kelvin to Degree Centigrade.



Thank you


EDA
EGYPTIAN DRUG AUTHORITY
هيئة الدواء المصرية


CPD
CENTER FOR CONTINUING
PROFESSIONAL DEVELOPMENT
مركز التطوير المهني المستمر

04-12-2023







Good Documentation practice



Presented by:

Ph. Mohamed Magdy Arafa

Periodic inspection follow up unit manager

Content

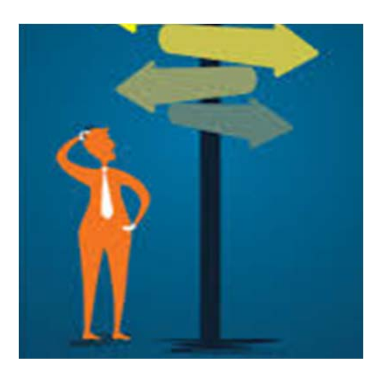
1. Types of documentation
2. Designing SOP
3. Good Documentation practice
4. Examples of documents



Descriptive documents



Descriptive documents give *instructions* on how to perform a procedure or a study, or give a description of specifications. The instruction type documents are: standard operating procedures (SOP); protocols (for validation studies, stability studies, safety studies); and master formulae (manufacturing instructions)





Forms for recording



form used for recording data as it is taken during the performance of tasks, tests, or events. These are forms (datasheets, or data record forms), reports, batch processing records, and equipment log books. These documents provide the evidence that the raw materials, facility environment, the production process, and the final product consistently meet the established quality requirements







There are also the identification systems or codes devised to number and track both information and documents. These are SOP numbers, equipment numbers, form numbers, receiving codes, and batch/lot numbers. These numbering systems should be designed so that procedures, processes and materials can be traced throughout the data record



The data on which these decisions are based should therefore be complete as well as being attributable, legible, contemporaneous, original and accurate, commonly referred to as "ALCOA".

Data



means all original records and true copies of original records, including source data and metadata and all subsequent transformations and reports of these data, which are generated or recorded at the time of the GXP activity and allow full and complete reconstruction and evaluation of the GXP activity.

Data



Data may be contained in paper records (such as worksheets and logbooks), electronic records and audit trails, photographs, microfilm or microfiche, audio- or video-files or any other media whereby information related to GXP activities is recorded.



Attributable. Attributable means information is captured in the record so that it is uniquely identified as executed by the originator of the data (e.g. a person or a computer system).



Legible, traceable and permanent.

The terms legible and traceable and permanent refer to the requirements that data are readable, understandable, and allow a clear picture of the sequencing of steps or events in the record so that all GXP activities conducted can be fully reconstructed by the people reviewing these records at any point during the records retention period set by the applicable GXP.



Contemporaneous. Contemporaneous data are data recorded at the time they are generated or observed.



Original.

Original data include the first or source capture of data or information and all subsequent data required to fully reconstruct the conduct of the GXP activity.



Accurate.

The term “accurate” means data are correct, truthful, complete, valid and reliable



Implicit in the requirements for ALCOA are that the records should be complete, consistent, enduring and available (to emphasize these requirements, this is sometimes referred to as ALCOA-plus).





Data integrity is the degree to which data are complete, consistent, accurate, trustworthy and reliable and that these characteristics of the data are maintained throughout the data life cycle.



Good Documentation Practice



Good documentation practices are those measures that collectively and individually ensure documentation, whether paper or electronic, is secure, attributable, legible, traceable, permanent, contemporaneously recorded, original and accurate.

Good documentation practice



- Good documentation constitutes an essential part of the quality assurance system and is key to operating in compliance with GMP requirements.
- Documentation may exist in a variety of forms, including paper-based, electronic or photographic media.
- There are two primary types of documentation used to manage and record GMP compliance: instructions (directions, requirements) and records/reports.
- Accuracy, integrity, availability and legibility of documents should be ensured.

Good documentation practice



- All types of document should be defined and adhered to.

(hybrid &homogenous forms documents, integrity throughout the retention period)

- Documents should be designed, prepared, reviewed, and distributed with care.

(comply with the relevant parts of Product Specification Files, Manufacturing and Marketing Authorization dossiers)

- Documents containing instructions should be approved, signed and dated by appropriate and authorized persons.

(effective date should be defined)

- Signatures should be in permanent indelible ink, no scanned signatures, no stamp in lieu of handwritten signature.





- Instructions should be laid out in an orderly fashion and be easy to check. The style and language of documents should fit with their intended use.
- Documents should not be hand-written; although, where documents require the entry of data, sufficient space should be provided for such entries.
- No spaces for hand written are left blank, if unused, they are crossed out or N/A entered.
- Handwritten entries should be made in clear, legible, indelible way.(no pencil is allowed)
- Any alteration made to the entry on a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded. White correction pen is not allowed

Good documentation practice



- Storage of critical records must at secure place, with access limited to authorized persons. The storage location must ensure adequate protection from loss, destruction, or falsification, and from damage due to fire, water, etc.

- Date may be recorded by electromagnetic or photographic means, but detailed procedures relating to whatever system is adopted must be available (AFP). Accuracy of the record should be checked as per the defined procedure. If documentation is handled by electronic data processing methods, only authorized persons should be able to enter or modify data in the computer, access must be restricted by passwords or other means, and entry of critical data must be independently checked.(also history must be maintained for alterations and deletions)



-restricting the ability to change any clock used for recording timed events, for example, system clocks in electronic systems and process instrumentation.

-ensuring controlled forms used for recording GXP data (e.g. paper batch records, paper case report forms and laboratory worksheets)



- controlling the issuance of blank paper templates for data recording of GXP activities so that all printed forms can be reconciled and accounted for.
- restricting user access rights to automated systems to prevent (or audit trail) data amendments.
- ensuring automated data capture or printers are attached and connected to equipment, such as balances, to ensure independent and timely recording of the data



- ensuring proximity of printers to sites of relevant activities;
- ensuring ease of access to locations of sampling points (e.g. sampling points for water systems) to allow easy and efficient performance of sampling by the operators and therefore minimizing the temptation to take shortcuts or falsify samples;
- ensuring access to original electronic data for staff performing data checking activities.



Data and record media should be durable. For paper records, the ink should be indelible. Temperature-sensitive or photosensitive inks and other erasable inks should not be used. Paper should also not be temperature-sensitive, photosensitive or easily oxidizable.

If this is not feasible or limited (as may be the case in printouts from legacy printers of balance and other instruments in quality control laboratories), then true or certified copies should be available until this equipment is retired or replaced.



Personnel should be trained in data integrity policies and agree to abide by them. Management should ensure that personnel are trained to understand and distinguish between proper and improper conduct, including deliberate falsification, and should be made aware of the potential consequences.



To assure the integrity of electronic data, computerized systems should be validated at a level appropriate for their use and application. Validation should address the necessary controls to ensure the integrity of data, including original electronic data and any printouts or PDF reports from the system.



Data life cycle. Validation should include assessing risk and developing quality risk mitigation strategies for the data life cycle, including controls to prevent and detect risks throughout the steps of:

■■ data generation and capture;

■■ data transmission;

■■ data processing;

■■ data review;

■■ data reporting, including handling of invalid and atypical data;

■■ data retention and retrieval;

■■ data disposal.





An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

Designing SOP



OBJECTIVE:

To lay down procedure for the preparation of Standard Operating Procedures.

SCOPE:

This procedure is applicable to all the SOP‟s throughout the organization.

RESPONSIBILITY:

Person Performing: Respective HOD‟s of concerning departments

Person Monitoring: QA officer/ HOD QA

PROCEDURE:

All SOP‟s shall be computer typed using Times New Roman font.

Format of SOP shall be as per Annexure SOP/QA/002/1.



Each SOP has:

I) Header,

II) Signature block

III) Body





Header: Present on all the pages of SOP and includes Company Logo, Name, address & Concerned Dept.: Company Logo, (In capital bold letters of font size 16)



Document Type: Standard Operating Procedure
(In capital bold letters of font size 14)
Ref. No. :It is like SOP/DC/YYY-Z
Where DC depicts the department code as below:
PE: Personnel Department
PD: Production Department
MT: Maintenance Department
QA: Quality Assurance Department
QC: Quality Control Department
ST: Store Department PU: Purchase Department



YYY is the sequential number starting from 001 for each department. And Z is the revision status, starting from 0 for the original version and 1 for the next version and so on. (In capital letters of font size 12). Supersedes: It is the Ref. No. of the earlier version. (In capital letters of font size 12).

Effective Date: It is the date from which the SOP shall be put in use. The date format has to be DD/MM/YYYY, where DD indicates the date, MM indicates the month & YYYY indicates the year (e.g. 01/11/2007). Date shall be written with blue indelible ink pen.



Review Date: It is the Month & Year during which the SOP shall be revised e.g. 21/2013, written with blue indelible ink pen. It shall be maximum 2 years from the effective date.

Page No.: It is like X OF Y. Where X is the individual page number and Y is the total number of pages. (In capital letters of font size 12)

Title: It shall be clear and descriptive. (In bold capital letters of font size 12).



Signature Block: It shall be below the header and only on the first page of the SOP. (Titles in the rows & columns shall be in bold letters & other text in normal letters of font size 12. Name and designation shall be typed. And signature and date shall be put in blue indelible ink pen)

Prepared by: Signature with date, name and designation of the person from user department who has drafted the SOP.

Reviewed by: Signature with date, name and designation of the HOD or the person from user department who has verified the draft of the SOP.

Approved by: Signature with date, name and designation of the person authorizing SOP, DGM QA or HOD QA.



Body: It shall contain the subject matter, which is written in the following Manner.

(Subtitles in capital bold letters and text matter in normal letters of font size 12).

OBJECTIVE: It shall define the purpose of the SOP.

SCOPE: It shall define the area of application.



SOPs and associated records of actions taken or, where appropriate, conclusions reached should be available for:

(a) equipment assembly and validation;

(b) analytical apparatus and calibration;

(c) maintenance, cleaning and sanitization;

(d) personnel matters including qualification, training, clothing and hygiene;

(e) environmental monitoring



f) pest control;

(g) complaints;

(h) recalls;

(i) returns.





-There should be SOPs and records for the receipt of each delivery of starting material and primary and printed packaging material.

-The records of the receipts should include:

(a) the name of the material on the delivery note and the containers;

(b) the “in-house” name and/or code of material if different from (a);

(c) the date of receipt;



(d) the supplier's name and, if possible, manufacturer's name;

(e) the manufacturer's batch or reference number;

(f) the total quantity, and number of containers received;

(g) the batch number assigned after receipt;

(h) any relevant comment (e.g. state of the containers).



-There should be SOPs for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

-SOPs should be available for each instrument and piece of equipment (e.g. use, calibration, cleaning, maintenance) and placed in close proximity to the equipment.

-There should be SOPs for sampling, which specify the person(s) authorized to take samples



-There should be an SOP describing the details of the batch (lot) numbering system, with the objective of ensuring that each batch of intermediate, bulk or finished product is identified with a specific batch number.

-The SOPs for batch numbering that are applied to the processing stage and to the respective packaging stage should be related to each other.

-The SOP for batch numbering should ensure that the same batch numbers will not be used repeatedly; this applies also to reprocessing.



-There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded.



-Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by an authorized person.

-Records should be maintained of the distribution of each batch of a product in order, for example, to facilitate the recall of the batch if necessary.



-Records should be kept for major and critical equipment, as appropriate, of any validations, calibrations, maintenance, cleaning or repair operations, including dates and the identity of the people who carried out these operations.

-The use of major and critical equipment and the areas where products have been processed should be appropriately recorded in chronological order.



There should be written procedures assigning responsibility for cleaning and sanitation and describing in sufficient detail the cleaning schedules, methods, equipment and materials to be used and facilities and equipment to be cleaned. Such written procedures should be followed.



-Master record. A document or set of documents that serve as a basis for the batch documentation (blank batch record).

-Batch records. All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

Master formula



A formally authorized master formula should exist for each product and batch size to be manufactured.

The master formula should include:

(a) the name of the product, with a product reference code relating to its specification;

(b) a description of the dosage form, strength of the product and batch size;

(c) a list of all starting materials to be used (if applicable with the INNs), with the amount of each, described using the designated name and a reference that is unique to that material (mention should be made of any substance that may disappear in the course of processing);



(d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable;

(e) a statement of the processing location and the principal equipment to be used;

(f) the methods, or reference to the methods, to be used for preparing and operating the critical equipment, e.g. cleaning (especially after a change in product), assembling, calibrating, sterilizing, use;



(g) detailed step-wise processing instructions (e.g. checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures);

(h) the instructions for any in-process controls with their limits;

(i) where necessary, the requirements for storage of the products, including the container, the labelling, and any special storage conditions;

(j) any special precautions to be observed.



Batch processing records



-should be kept for each batch processed.

-It should be based on the relevant parts of the currently approved specifications on the record.

-The method of preparation of such records should be designed to avoid errors. (Copying or validated computer programs are recommended. Transcribing from approved documents should be avoided.)



During processing, the following information should be recorded at the time each action is taken, and after completion the record should be dated and signed by the person responsible for the processing operations.

(a) the name of the product;

(b) the number of the batch being manufactured;

(c) dates and times of commencement, of significant intermediate stages, and of completion of production;



(d) the name of the person responsible for each stage of production;
(e) the initials of the operator(s) of different significant steps of production and, where appropriate, of the person(s) who checked each of these operations (e.g. weighing);



(f) the batch number and/or analytical control number and the quantity of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
(g) any relevant processing operation or event and the major equipment used;
(h) the in-process controls performed, the initials of the person(s) carrying them out, and the results obtained;



(i) the amount of product obtained at different and pertinent stages of manufacture (yield), together with comments or explanations for significant deviations from the expected yield;

(j) notes on special problems including details, with signed authorization for any deviation from the master formula.



Packaging instructions



Formally authorized packaging instructions should exist for each product, pack size and type. These should normally include, or make reference to:

(a) the name of the product;

(b) a description of its pharmaceutical form, strength and, where applicable, method of application;

(c) the pack size expressed in terms of the number, weight or volume of the product in the final container;



(d) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications for each packaging material;

(e) where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product have been marked;



(f) special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before and after packaging operations;

(g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;

(h) details of in-process controls with instructions for sampling and acceptance limits.



Batch packaging record



-A batch packaging record should be kept for each batch or part batch processed.

-It should be based on the relevant parts of the approved packaging instructions, and the method of preparing such records should be designed to avoid errors. (Copying or validated computer programs are recommended. Transcribing from approved documents should be avoided.)



Before any packaging operation begins, checks should be made that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use. These checks should be recorded.



The following information should be recorded at the time each action is taken, and the date and the person responsible should be clearly identified by signature or electronic password:

(a) the name of the product, the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained and the reconciliation;

(b) the date(s) and time(s) of the packaging operations;



(c) the name of the responsible person carrying out the packaging operation;

(d) the initials of the operators of the different significant steps;

(e) the checks made for identity and conformity with the packaging instructions, including the results of in-process controls;



(f) details of the packaging operations carried out, including references to equipment and the packaging lines used, and, when necessary,

the instructions for keeping the product if it is unpacked or a record of returning product that has not been packaged to the storage area;

(g) whenever possible, samples of the printed packaging materials used, including specimens bearing the approval for the printing of and regular check (where appropriate) of the batch number, expiry date, and any additional overprinting;



(h) notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person;

(i) the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of product obtained to permit an adequate reconciliation.



(i) the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of product obtained to permit an adequate reconciliation.



Production records should be reviewed as part of the approval process of batch release before transfer to the authorized person. Any divergence or failure of a batch to meet production specifications should be thoroughly investigated. The investigation should, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy. A written record of the investigation should be made and should include the conclusion and follow-up action.

Validation Master Plan



A Validation Master Plan is a document that summarises the firm's overall philosophy, intentions and approach to be used for establishing performance adequacy.

Product quality review (annual product review)



Regular, periodic or rolling quality reviews of all pharmaceutical products, including export-only products, should be conducted with the objective of verifying the consistency of the existing process and the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements.



Complaints



All complaints and other information concerning potentially defective products should be carefully reviewed according to written procedures and the corrective action should be taken.



All decisions made and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.



There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.

Product recall



-There should be a system to recall from the market, promptly and effectively, products known or suspected to be defective.

-The authorized person should be responsible for the execution and coordination of recalls. He or she should have sufficient staff to handle all aspects of the recalls with the appropriate degree of urgency.



There should be established written procedures, which are regularly reviewed and updated, for the organization of any recall activity.

Recall operations should be capable of being initiated promptly down to the required level in the distribution chain.



The distribution records should be readily available to the authorized person, and they should contain sufficient information on wholesalers and directly supplied customers (including, for exported products, those who have received samples for clinical tests and medical samples) to permit an effective recall.



The progress of the recall process should be monitored and recorded.

Records should include the disposition of the product. A final report should be issued, including a reconciliation between the delivered and recovered quantities of the products.

Contract production, analysis and other activities



Contract production, analysis and any other activity covered by GMP must be correctly defined, agreed and controlled in order to avoid misunderstandings that could result in a product, or work or analysis, of unsatisfactory quality.

Self-inspection, quality audits and suppliers' audits and approval



The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and QC. The self inspection programme should be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions.



Self-inspections should be performed routinely, and may be, in addition, performed on special occasions, e.g. in the case of product recalls or repeated rejections, or when an inspection by the health authorities is announced



Suppliers' audits and approval



The person responsible for QC should have responsibility, together with other relevant departments, for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.

Training



The manufacturer should provide training in accordance with a written programme for all personnel whose duties take them into manufacturing areas or into control laboratories (including the technical, maintenance and cleaning personnel) and for other personnel as required.



Personal hygiene



-All personnel, prior to and during employment, as appropriate, should undergo health examinations.

-Personnel conducting visual inspections should also undergo periodic eye examinations.



Validation protocol



-A document describing the activities to be performed in a validation, including the acceptance criteria for the approval of a manufacturing process - or a part thereof - for routine use..



Validation report



-A document in which the records, results and evaluation of a completed validation programmed are assembled. It may also contain proposals for the improvement of processes and/or equipment.

Audit trail



The audit trail is a form of metadata that contains information associated with actions that relate to the creation, modification or deletion of GXP records. An audit trail provides for secure recording of life-cycle details such as creation, additions, deletions or alterations of information in a record, either paper or electronic, without obscuring or overwriting the original record.

An audit trail facilitates the reconstruction of the history of such events relating

to the record regardless of its medium, including the “who, what, when and why”

of the action.

Back up



A backup means a copy of one or more electronic files created as an alternative in case the original data or system are lost or become unusable

(for example, in the event of a system crash or corruption of a disk).

References



-WHO “World Health Organization” TRS “Technical Report Series” 986 annex 2 “main principles”, 2014

-A WHO guide to good manufacturing practice (GMP) requirements Part 1: Standard operating procedures and master formulae

-Bhattacharya J. : Guidance for Preparing Standard Operating Procedures (Sops), OSR Journal Of Pharmacy, Volume 5, Issue 1 (January 2015), PP. -29-36

-PIC/S Recommendations on Validation master plan installation and operational qualification non-sterile process validation cleaning validation

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- WHO, QAS Terminology db - List of Terms and related guidelines.

- WHO, TRS 996 annex 5, Guidance on good data and record management practices, 2016


Thank you
CPD
EDA
EGYPTIAN DRUG AUTHORITY


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هيئة الدواء المصرية


CPD
CENTER FOR CONTINUING
PROFESSIONAL DEVELOPMENT
مركز التطوير المهني المستمر





Water for Pharmaceutical Use

Dr. Mohamed Magdy arafa
Periodic inspection follow up unit manager

Agenda



1. Part 1: Reviewing water treatment systems
2. Part 2:

Storage and distribution requirements.

3. Part 3: WFI production &Pure steam
4. Part 4: Qualification & Monitoring &Sampling.
5. Part 5: Inspection of water system



1. Part 1: Reviewing water treatment systems
2. Part 2:Storage and distribution requirements.
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General

- Part 1 – reviewed types of water and water purification systems
- Water can be used directly, or stored in a storage vessel for subsequent distribution to points of use
- Design appropriately to prevent recontamination after treatment
- Combination of on-line and off-line monitoring to ensure compliance with water specification

Pretreatment section & System Design.

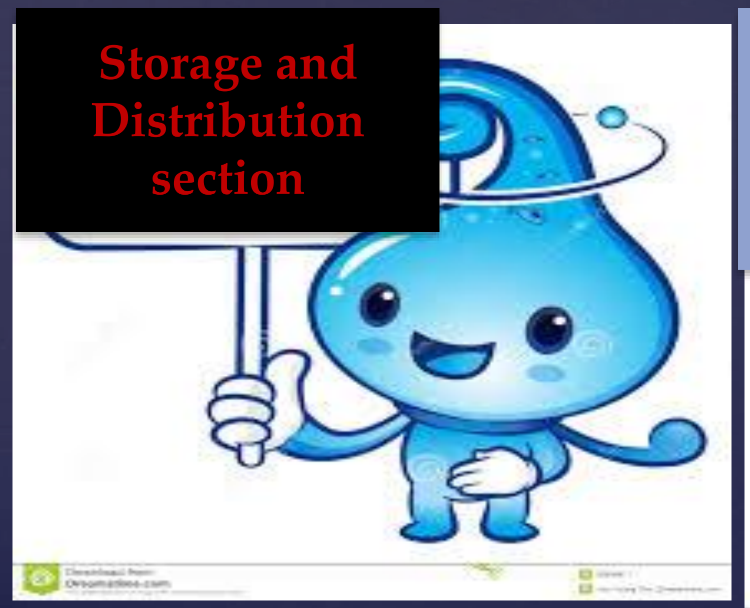


1) Drawing of P&ID
2) Purified water Chemical and microbial Limits.
3) Design of Purified water system.
   1) Pretreatment section
      A. Raw water tank
      B. Injection of NaOCl
      C. Particles removable according to the Egyptian water specs
      D. Sand filter
      E. Softeners
      F. Depth filter selection

Sections of purified water system .



Purified water system consists of :-







What is P&ID means?



- A piping and instrumentation diagram (**P&ID**) is a detailed diagram in the process industry which shows the piping and vessels in the process flow, together with the instrumentation and control devices.

What P&ID can Covering ?



3- Piping and Instrumentation Diagram (P&ID)

- *For **Equipment—Show** Every Piece* (spare units, parallel units, summary details of each unit)
- *For **Piping—Include** All Lines* (drains, sample connections and specify size (use standard sizes), materials of construction, insulation (thickness and type)
- *For **Instruments**—*Identify indicators, recorders, controllers
- *For **Utilities**—*Identify entrance utilities, exit utilities, exit to waste treatment facilities



Water for Pharmaceutical USE

Chemical limits

Microbial limits

Purified water Conductivity limits:



Conductivity of PWS (USP 37,645)

- *Stage 1* ***is intended for online***
- *measurement or may be* performed offline in a suitable container.

Conductivity **NMT 1.3 µS/cm at 25 C**. If not proceed to stage 2.

Stage 2: ***is intended for Offline Lab testing***

If the conductivity **is not greater than 2.1 µS/cm**, the water meets the requirements of the test for conductivity.

If the conductivity is greater than 2.1 µS/cm, proceed with Stage 3

Conductivity of PWS (USP 37,645)



Stage 3: IF conductivity **is not greater than 2.4 µS/cm at pH 6** . The water meets the requirements of the test for conductivity. If either the measured conductivity is greater than this value or the pH is outside the range of 5.0±7.0, the water does not meet the requirements of the test for conductivity.



USP vs BP / EP



Parameter	Unit	USP	Ph. Eur. (Bulk)
TOC	ppb C	500	500
Conductivity	µS/cm @ 20 °C	-	≤ 4.3
Conductivity	µS/cm @ 25 °C	≤ 1.3	-
Nitrate (NO_3)	ppm	-	≤ 0.2
Heavy Metals	ppm as Pb	-	≤ 0.1
Aerobic Bacteria	CFU/ ml	≤ 100	≤ 100

Purified water Chemical and microbial Limits.



Suggested bacterial limits *(CFU /mL)(WHO ,2005)*

Sampling location	Target	Alert	Action
Raw water	200	300	500
Post multimedia filter	100	300	500
Post softener	100	300	500
Post activated carbon filter	50	300	500
Feed to RO	20	200	500
RO permeate	10	50	100
	1	10	100

Purified water purification



Sequence of techniques

Pretreatment + DI
Pretreatment + RO 1+DI
Pretreatment +RO1 + RO2
Pretreatment +RO1+EDI
Pretreatment +RO1+RO2+EDI



1. Part 1: Reviewing water treatment systems
2. Part 2:Storage and distribution requirements.
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Water storage and distribution systems



- The storage and distribution system should be considered as a **key part** of the whole system and should be designed to be fully integrated with the water purification components of the system.

Jointing as an example of Engineering points of Water Loops



- the selected system materials should be easily joined by welding in a controlled manner.
- the control of the process should include, as a minimum, qualification of the operator, documentation of the welder set-up, work session test pieces (coupons), logs of all welds and visual inspection of a defined proportion of welds, e.g.
  - 100% hand welds, 10% automatic welds.

Materials. What type and where in water system could be applied ?



- Materials. Suitable materials that may be considered for sanitary
- elements of the system include 316L (low carbon) stainless steel,
- polypropylene, polyvinylidene-di$uoride and per$uoroalkoxy. !e
- choice of material should take into account the intended sanitization
- method. Other materials such as unplasticized polyvinyl-chloride
- (uPVC) may be used for treatment equipment designed for less pure
- water such as ion exchangers and so%eners.

Major Stainless Steel Grades - Used in Ethanol Plants

Common Name	UNS	EN	Attributes
304	S30400	1.4301	Good general corrosion resistance to slightly acidic as well as caustic media. Minimum strength level slightly higher than for the L grades.
304L	S30403	1.4307	As above, but L grades are preferred for welded constructions. Material can be usually purchased as dual certified, meeting the requirements of both 304 and 304L.
316	S31600	1.4401/ 1.4436	Improved corrosion resistance in most acidic conditions, especially at higher temperatures and/or with chlorides present
316L	S31603	1.4404/ 1.4432	As above, but L grades are preferred for welded constructions. Material can be usually purchased dual certified, meeting the requirements of both 316 and 316L.



Composición del acero inoxidable 304-304L-316-316L								
AISI	Cr	Ni	Mo	Mn	Si	C	P	S
304	16.00-18.00	8.00-10.00	-	2.00	0.75	0,08	0.045	0.030
304L	16.00-18.00	8.00-13.00	-	2.00	0.75	0,035	0.045	0.030
316	16.00-18.00	10.00-14.00	2.00-3.00	2.00	0.75	0.08	0.045	0.030
316L	16.00-18.00	10.00-15.00	2.00-3.00	2.00	0.75	0.035	0.045	0.030





Contact materials include:

- *Pipes*
- *Valves and fittings*
- *Seals*
- *Diaphragms and instruments*
- *Tanks*
- *Pumps, etc.*

Proper selection to ensure these are suitable



WPU system contact materials (2)

- **Factors to consider (including components)**
  - *Compatibility and leaching effect*
  - *Corrosion resistance*
  - *Smooth internal finishing, ease of jointing*
  - *Hygienic / sanitary design*
  - *Documentation*
  - *Materials of construction (MOC) - (including original/certified copies of material certificates*



WPU system contact materials (3)

- Compatibility
  - *With temperature and chemicals used in the system*
- Leaching effect
  - *Non-leaching at temperature range*
- Corrosion resistance
  - *PW, HPW, WFI highly corrosive*
  - *Stainless steel Grade 316L to be used*
  - *System passivated after installation and modification according to SOP*



WPU system contact materials (4)

- Smooth internal finish
  - *Biofilms and microbial contamination*
  - *Crevices and roughness result in problem areas associated with contamination and corrosion*
  - *Internal finish to have arithmetical average surface roughness not greater than 0.8 micrometer arithmetical mean roughness (Ra)*
  - *Mechanical and electropolishing needed when stainless steel is used*



WPU system contact materials (5)

- Joints
  - *System materials easily jointed, e.g. by welding*
  - *Process controlled including requirements such as:*
    - ***Qualification of operator***
    - ***documentation of welder set up***
    - ***work session test pieces***
    - ***weld logs***
    - ***visual inspection of defined proportions of welds***



WPU system contact materials (6)

- Suitable materials include:
  - *Stainless steel Grade 316L (low carbon)*
  - *Polypropylene (PP)*
  - *Polyvinylidenedifluoride (PVDF)*
  - *Perfluoroalkoxy (PFA)*
- Unplasticized polyvinylchloride (uPVC) used for *non-hygienic* designed water treatment equipment such as ion exchangers and softeners



System sanitization and bioburden control

- Systems in place to control proliferation of microbes
- Techniques for sanitizing or sterilization
- Consideration already during design stage – then validated
- Special precautions if water not kept in the range of 70 to 80 degrees Celsius



Storage and distribution - *Storage vessels*

- Design and size important:
  - *Serves as buffer between generation and use*
  - *Avoid inefficiencies and equipment stress during frequent on-off cycles*
  - *Short-term reserve in case of failure*
- Contamination control consideration
  - *Headspace (kept wet with spray ball / distributor device)*
  - *Nozzles (no dead zone design)*
  - *Vent filters (type, testing, use of heat)*
  - *Pressure relief valves and burst discs (sanitary design)*



Storage and distribution – *Pipes and heat exchangers*

- Continuous circulating loop needed
- Filtration not recommended in loop and take-off point
- Heat exchangers:
  - *Double tube plate or double plate and frame type*
  - *Designed to ensure no stasis of water*
- Where water is cooled before use, done in minimum time, and validated process



Storage and distribution – *Circulation pumps*

- Sanitary design with appropriate seals
- Standby pumps
  - *Can be used*
  - *Configured or managed in a way to avoid trapped dead zones*



Typical water storage and distribution schematic

Feed Water from DI or RO

Cartridge filter 1 µm

Heat exchanger

Spray ball

Hydrophobic air filter & burst disc

Water must be kept circulating

UV light

Outlets

Ozone Generator

Heat Exchanger

Hygienic pump

Air break to drain



Biocontamination control techniques

- Continuous turbulent flow circulation
  - *Specified velocity proven (qualification), and monitored*
- Avoid dead legs
- Hygienic pattern diaphragm valves
- Shortest possible length of pipe work
- Pipe work of ambient temperature systems, isolated from hot pipes

Biocontamination control techniques (2)





There should be no dead legs

If D=25mm & distance X is
greater than 50mm, we have
a dead leg that is too long



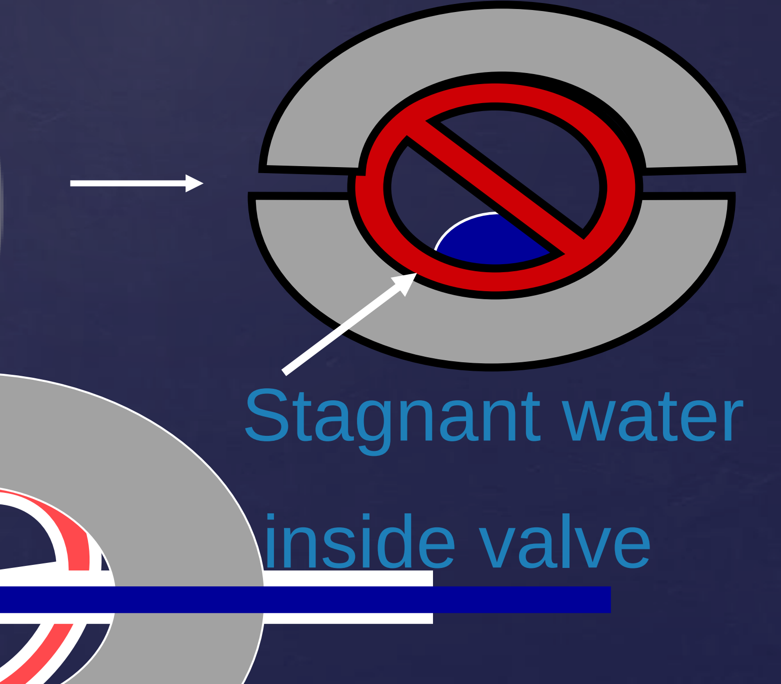
Biocontamination control techniques (3)

1. Ball valves are unacceptable



2. Bacteria can grow when the valve is closed

3. The water is contaminated as it passes through the valve





Biocontamination control techniques (4)

- Pressure gauges separated from system membranes
- Pipe work laid to fall (slope) – allows drainage
- Maintain system at high temperature (above 70 degrees Celsius)
- Use UV radiation
  - *Flow rate, life-cycle of the lamp*
- Suitable construction material



Biocontamination control techniques (5)

- Periodic sanitization with hot water
- Periodic sanitization with super-heated hot water or clean steam
  - *Reliable*
  - *Monitoring temperature during cycle*
- Routine chemical sanitization using, e.g. ozone
  - *Removal of agent before use of water important*



1. Part 1: Reviewing water treatment systems
2. Part 2:Storage and distribution requirements.
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Water for Injection



Part one:-

1. What is (WFI)?
2. Specifications of WFI
3. WFI generation system
4. WFI Distribution loop: Heat-Exchanger installation
5. Cleaning and Sanitization of WFI system

Part two:-

1. Production of pure steam .
1. Specs of Pure steam (Clean Steam)
2. Guideline and standards of pure steam
3. Main system Configuration of pure steam

What is (WFI)?



- Water for Injections (WFI)
- Prepared from potable water source or PW (preferred)
- WFI is not a final dosage form
- WFI is an intermediate bulk product
- According to The International and European Pharmacopoeias – final purification step should be distillation why ?

Specifications of WFI according to USP requirements



- WFI must meet USP requirements in the distribution system and at the various drops.

  Requirements include meeting the following specifications:

1. TOC Specification of **< 500 ppb (Alert > 250 ppb, Action > 350 ppb).**
2. Conductivity (On-Line) to meet USP WFI requirements adjusted for temperature **(nominal conductivity <1.3 µS/cm at 25o C to pass Stage 1** requirements).
3. Endotoxin levels **≤ 0.25 EU/mL (Alert ≥ 0.06 EU/mL, Action ≥ 0.12 EU/mL).**
4. Total Viable Organisms **≤ 10 CFU / 100 mL (Alert ≥ 5 CFU / 100 mL, Action ≥ 10 CFU / 100 mL**

Specifications of WFI according to USP requirements



❖ Standard USP water specifications for pharmaceuticals manufacturing are:-

PWS Specs:-

- **conductivity 0.2–1.0 µS/cm at 25 C;**
- **pH5.0–7.0;**
- **TOC level <500ppb;**
- **Bacteria count <100cfu/100ml.**

WFI SPECS:-

- bacteria count <10cfu/100 ml and Endotoxin level 0.25EU/ml.

Specifications of WFI according to USP requirements



Water for Injection

Parameter	Unit	USP	Ph. Eur. (Bulk)
TOC	ppm C	0.50	0.5
Conductivity	µS/cm@20°C	–	≤ 1.1
Conductivity	µS/cm@25°C	≤ 1.3	–
Nitrate (NO_3)	ppm	–	≤ 0.2
Aerobic bacteria	CFU/100ml	≤ 10	≤ 10
Bacterial endotoxins	EU/ml	≤ 0.25	–
Bacterial endotoxins	I.U./ml	–	≤ 0.25

1. WFI generation system : Falling film methods



WFI Distribution loop: Heat-Exchanger installation



H

RO/DI WATER

WFI GENERATION

HOT WFI USERS

WFI STORAGE TANK

AMBIENT WFI USERS

HEAT EXCHANGER

CH. WATER RETURN

CH. WATER SUPPLY

WFI Distribution loop: Heat-Exchanger installation



RO/DI WATER
WFI GENERATION
RECIRC LOOP
WFI STORAGE TANK
HOT AND AMBIENT WFI USERS
HEAT EXCHANGER
CHWR
CHWS
HEAT EXCHANGER
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H

WFI Distribution loop: Heat-Exchanger installation



WFI GENERATION
RECIRC LOOP
WFI STORAGE TANK
HOT AND AMBIENT WFI USERS
HEAT EXCHANGER
HEAT EXCHANGER
HEAT EXCHANGER
HEAT EXCHANGER

Cleaning and Sanitization of WFI system



- The WFI Storage and Distribution Systems are effectively self sanitizing and self cleaning.
- On start-up, water from the WFI Generator is directed to waste until it meets specification.

This feature is self contained on the condensing unit.

- The WFI Storage and Distribution Systems are periodically passivated to reduce corrosion.
- The WFI Storage and Distribution Systems are periodically de-rouged to maintain smooth, clean surfaces and reduce the potential for biological contamination.

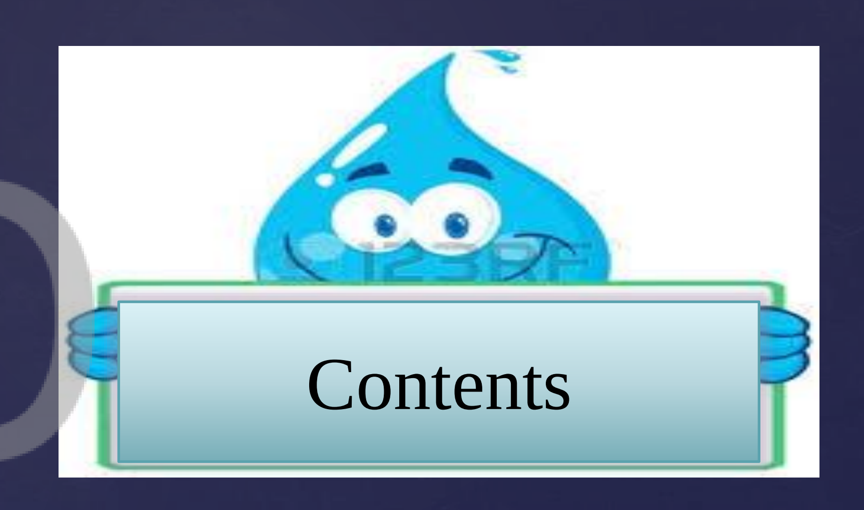
Content



1. What is (WFI)?
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Part two:-

1. Production of pure steam .
1. Specs of Pure steam (Clean Steam)
2. Guideline and standards of pure steam
3. Main system Configuration of pure steam
4. Water system Validation .
5. Pure system qualification tests



Production of Pure steam (Clean Steam)



Pure Steam (PS)

Pure steam is evaporated above 120°C and used for humidification and sterilization of e.g. porous goods.

The level of steam saturation or dryness, and the amount of non-condensable gases are to be determined by the Pure Steam application. The condensate must comply with the respective WFI requirements.



Specs of Pure steam (Clean Steam)

Pure Steam (condensate)			
Parameter	**Unit**	**USP**	**Ph. Eur. (Bulk)**
TOC	ppm C	0.50	n.c.st.
Conductivity	µS/cm@25°C	≤ 1.3	n.c.st.
Aerobic bacteria	CFU/100ml	≤ 10	n.c.st.
Bacterial endotoxins	EU/ml	≤ 0.25	n.c.st.

Main Configuration of pure steam



Pure steam

Fine separation - bell separator

Coarse separation

Feed water inlet

Double pipe floor

Downpipe

Insulation pipe

Heat exchanger

Pure steam system



- Generators are classified according to:
  - The natural circulation procedure
  - Downdraft procedure and
  - Pure steam generators with an external heat exchanger.

- In order to remove non-condensable gases from the steam, the pure steam generator is fitted with an upstream degassing device.

- The design of a distribution system must take into account any thermal expansion.
  - To avoid combustion and minimize energy loss, sufficient insulation is essential.



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Start up and commissioning

- Precursor to qualification and validation
- Should be planned, well defined, well documented
- Includes setting to work
- Includes system set-up
- Includes recording of system performance parameters
- Controls loop tuning



Qualification

- WPU systems are "direct impact systems"
- Therefore stages to be considered in qualification should include DQ, IQ, OQ, PQ
- DQ: Design review influenced by source water and required water quality
- IQ: Installation verification of the system



Qualification

- OQ: operational qualification
- Presentation focusing on PQ
- PQ demonstrates consistent and reliable performance of the system
- Three phase approach recommended over extended period – proves reliability and robustness



Phase 1 (1):

- A test period of 2-4 weeks – monitoring the system intensively
- System to operate continuously without failure or performance deviation

The following should be included in the testing approach

- Undertake chemical and microbiological testing in accordance with a defined plan



Phase 1 (2)

- Sample daily:
  - *incoming feed-water*
  - *after each step in the purification process*
  - *each point of use and at other defined sample points*
- Develop:
  - *appropriate operating ranges*
  - *and finalize operating, cleaning, sanitizing and maintenance procedures*



Phase 1 (3)

- Demonstrate production and delivery of product water of the required quality and quantity
- Use and refine the standard operating procedures (SOPs) for operation, maintenance, sanitization and troubleshooting
- Verify provisional alert and action levels
- Develop and refine test-failure procedure



Phase 2. (1)

- A further test period of 2-4 weeks – further intensive monitoring the system
- Deploying all the refined SOPs after the satisfactory completion of phase 1
- Sampling scheme generally the same as in phase 1
- Water can be used for manufacturing purposes during this phase



Phase 2. (2)

Demonstrate:

- Consistent operation within established ranges
- Consistent production and delivery of water of the required quantity and quality when the system is operated in accordance with the SOPs

Phase 3.



- Over 1 year after the satisfactory completion of phase 2
- Water can be used for manufacturing purposes during this phase

Demonstrate:

  - *extended reliable performance*
  - *that seasonal variations are evaluated*

- Sample locations, sampling frequencies and tests should be reduced to the normal routine pattern based on established procedures proven during phases 1 and 2



On going system monitoring

- After phase 3 – system review needed
- Based on review including results, establish a routine monitoring plan
- Monitoring to include a combination of on-line monitoring and off-line sample testing
- Data analysed for trends



Ongoing system monitoring (2)

- Monitoring parameters to include:
  - *Flow, pressure, temperature, conductivity, TOC*
- Samples taken:
  - *From points of use, and specific sample points*
  - *In a similar way how water is used in service*
- Tests to include physical, chemical and microbial attributes



Maintenance

A controlled, documented maintenance programme covering:

- Defined frequency with plan and instructions
- Calibration programme
- SOPs for tasks
- Control of approved spares
- Record and review of problems and faults during maintenance



System review

- WPU (PW, HPW and WFI) systems to be reviewed at appropriate regular intervals
- Review team includes engineering, QA, operations and maintenance



System review (2)

- The review to cover, e.g.
  - *changes made since the last review*
  - *system performance*
  - *reliability*
  - *quality trends*
  - *failure events*
  - *investigations*
  - *out-of-specifications results from monitoring*
  - *changes to the installation*
  - *updated installation documentation*
  - *log books*
  - *the status of the current SOP lists*

Pure Steam System Qualification



Steam Quality Test Points

- In order to test the steam quality specific test points on the steam line are required
- Following fig. This test point is usually installed between the steam main supply isolating valve and the sterilizer.

The steam supply pipe



Minimum 400 mm of straight pipe

1/4" BSP (NPT for USA) socket for NC Gas test

1/4" BSP (NPT for USA) socket for pitot tube for Dryness and Superheat tests

1/4" BSP (NPT for USA) socket for temperature sensor used for the Dryness test

Direction of steam flow to the sterilizer

Acceptable criteria of pure steam test



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Endotoxin value: less than 0.25 EU/ml

- ✓ **Non-condensable gas test point ;**

  less than 3.5 %

- ✓ **Dryness Value ;**

  less than 5 % moisture content

- ✓ **Superheat Test Point ;**

  less than 25 C

Test # 0: Endotoxin value



Test # 1: Non-condensable gas



JOB Number :-

Calculation Format for the Pure Steam Quality Testing :-

(1) NON CONDENSABLE GAS :- Vg / Vc X 100 = — In % (Acceptable Limit = ≤ 3.5 %)

Here,
Vg = Volume of Gas in ml

Vc = Volume of Condensate in ml.

(2) DRYNESS FRACTION TEST :- (Acceptable Limit = ≥ 0.95)

$$D = \frac{(Tf - Ts) X [\{4.18 (Ms - Me)\} + 0.24]}{L X (MF - MS)} - \frac{(Ta - Tf) X 4.18}{L}$$

HERE,
Ts = INITIAL TEMPERATURE OF WATER IN FLASK IN °C

Tf = FINAL TEMPERATURE OF WATER AND CONDENSATE IN FLASK IN

Ta = TEMPERATURE OF PURE STEM DELIVERED IN °C

Me = INITIAL MASS OF EMPTY FLASK IN KG.

Ms = MASS OF EMPTY FLASK + 650 ML WATER IN KG.

Mf = MASS OF EMPTY FLASK + 650 ML WATER + CONDENSATE IN KG.

L = LATENT HEAT OF PURE STAM TEMPERATURE IN KJ/Kg.

4.18 CONSTANT

0.24 CONSTANT

(3) DEGREE OF SUPERHEAT :- Te – To = — °C (Acceptable Limit = ≤ 25°C)

HERE,
Te = TEMPERATURE OF PURESTEAM IN EXPANSION TUBE

To = WATER BOILING TEMPERATURE AT ATYMOSPHERIC PRESSURE (100 °C)

Test # 2: Dryness Value



Measurement of Dryness Value

Test # 2: Dryness Value



The dryness value describes the amount moisture present in steam.

If the steam is too dry there is a risk that it may superheat when entering the sterilizer and result in conditions where sterilization may not occur.

If steam has too much moisture, the loads and packaging may be wet at the end of the process.

Because bacteria can grow through wet packaging and moisture provides an environment for bacteria to grow, it would be normal to reject wet loads and reprocess them

Test # 3: Superheat Test Point



Superheated steam cause a risk to sterilization as it contains no moisture, which, combined with temperature, is essential for the coagulation of bacterial cell walls.



Measurement of **Superheat Value**

Test # 3: Superheat Test Point



The cause of superheated steam is usually as the result of large pressure drops between the steam distribution system and the sterilizer. EN 285 recommends that the pressure drop ratio should not exceed 2:1.



Measurement of **Superheat Value**



1. Part 1: Reviewing water treatment systems
2. Part 2:Storage and distribution requirements.
3. Part 3: WFI production &Pure steam
4. Part 4: Qualification & Monitoring &Sampling.
5. Part 5: Inspection of water system



Inspection of water purification systems



Prepare an aide-memoire for items to inspect:

- Schematic drawing review
- Changes to system since installation
- Sampling procedure and plan
- Specifications, results and trends
- Out-of-specification results
- Annual system review
- Deviations



Prepare an aide-memoire for items to inspect (2):



- Results of system performance monitoring
- Out of limit results, failure investigations and alarms recorded
- Sanitization procedures and records
- Maintenance and repairs logs/records
- Instrument calibration and standardization
- Qualification and validation including DQ, IQ, OQ, PQ
- Requalification when appropriate, etc.



Where to start:

What is the water to be used for?

- *sterile products*
- *non-sterile products, e.g. oral liquid products, external applications*
- *solid dosage forms*
- *washing and rinsing*

- Start: Document review – site verification – followed by additional document review





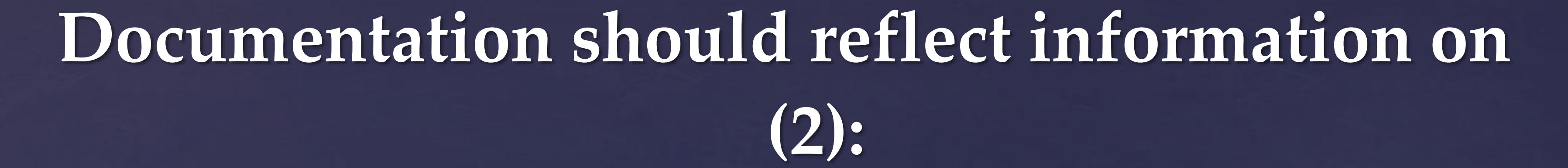
- Start with document review (e.g. schematic drawing of the system, "water quality manual" if available)
- Review change control (in case of changes after qualification and validation)
- On site verification (system in accordance with the drawing)
- Start source water supply
- Pre-treatment and treatment systems



Documentation should reflect information on:

- Pipeline
- Valves (non-return type)
- Breather points
- Couplings
- Pipe slope
- Velocities
- Sampling points
- Drain points
- Instrumentation
- Flow rates





Documentation should reflect information on (2):

- Specification for each system element
- Standard procedures for use
- System changes
- Routine and non-routine maintenance
- Investigations and corrective action
- Validation studies
- Chemical and microbiological specifications
- Sampling instructions
- Test procedures
- Responsible persons
- Training requirements



On site review and verification:

- Walk through the system, verifying the parts of the system as indicated in the drawing
- Review procedures and "on site" records, logs, results
- Verify components, sensors, instruments
- Inspect the finishing, state, calibration status, labels, pipes, tanks etc as discussed in previous parts of this module
- Start with source water supply – follow whole system "loop"



Well water

- Inspect exposed parts of the well, depth of well
- Check for nearby septic systems, hazardous materials usage (pesticides, fertilizers, etc.)
- Well maintenance



Raw water storage

- May be required prior to pre-treatment
- Check material of construction
  - *Concrete, steel are acceptable but check corrosion*
  - *Plastics or plastic linings may leach*
- Check cover
  - *To keep out insects, birds and animals*
- Check disinfection practices



Water treatment system inspection (1)

- Checks may include:
  - *dead legs*
  - *filters*
  - *pipes and fittings*
  - *Ionic beds*
  - *storage tanks*
  - *by-pass lines*



Water treatment system inspection (2)

- Checks may include:
  - *pumps*
  - *UV lights*
  - *sample points*
  - *reverse osmosis*
  - *valves*
  - *heat exchangers*
  - *Instruments, controls, gauges, etc.*



Other checks (1)

- Stainless steel – PVC and most plastics not recommended
- Weld quality
- Hygienic couplings
- Passivation
- Air breaks or "Tundish"

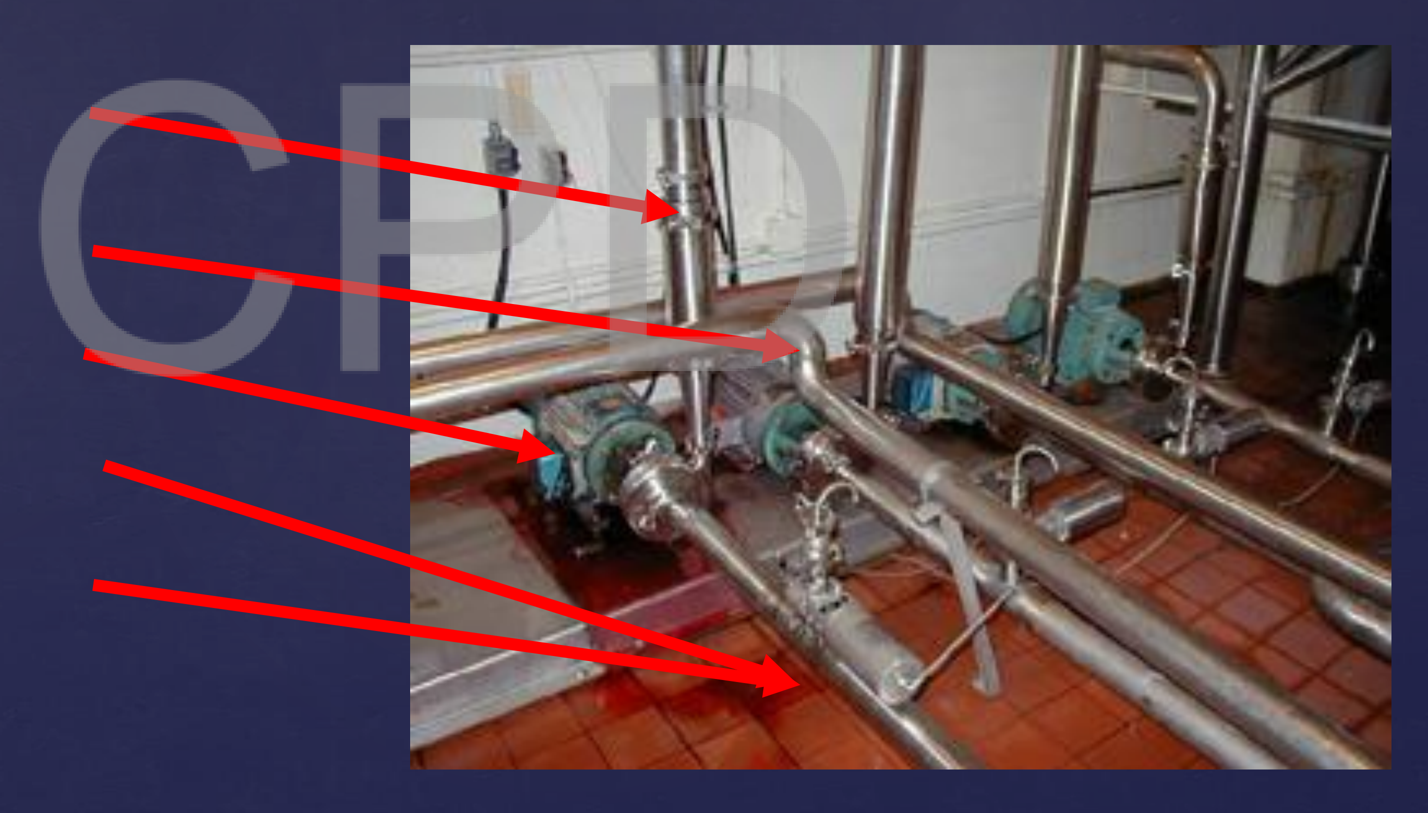




Other checks (2)

Pipes and pumps

- *hygienic couplings*
- *welded pipes*
- *hygienic pumps*
- *hygienic sampling points*
- *acceptable floor*
- *no leaks*





Other checks (3)

Check condition of equipment

Staining on water storage tanks





Corrosion on plates of heat exchangers indicates possible contamination



Other checks (3)

Check condition of equipment

Staining on water storage tanks





Corrosion on plates of heat exchangers indicates possible contamination



Other checks (4):

Maintenance records, maintenanc

of pump seals and O rings







Other checks (5)

Air filters

- Integrity testing, sterilization and replacement frequency
- Check burst discs





Other checks (6)

Zeolite water softener
exchanges Ca and Mg for Na

- Carefully check by-pass valves and lines
- These sometimes leak or are inadvertently left open
- A blanking piece is better during operation phase



Other checks (7)

- Activated carbon bed sanitization
- Temperature-compensated conductivity meters
- Influence of plastic pipe adhesive on TOC
- Non-condensable gases in pure steam



Other checks (8)

- Polypropylene welding inspection
  - *checking pin holes*
- Retrospective validation of WFI system
- Rouging of WFI storage systems
- Spray ball efficacy



Other checks (9)

- UV light – monitoring performance and lamp life and intensity
- Validating ozone dosage
- Specifications for acids, alkalis for DI and sodium chloride for water softener
- "Normally open" and "normally closed" valves



Then review additional documentation

- Qualification protocols and reports
- Change control request (where applicable)
- Requalification (where applicable)
- QC and microbiology laboratory:
- SOP for sampling
- Procedures and records



Sampling (1)

- There must be a sampling procedure
- Sample integrity must be assured
- Sampler training
- Sample point
- Sample size



Sampling (2)

- Sample container
- Sample label
- Sample transport and storage
- Arrival at the laboratory
- Test method
- When is the test started?



Testing

- Review method verification
- Chemical testing
- Microbiological testing
  - *test method*
  - *types of media used*
  - *incubation time and temperature*
  - *objectionable and indicator organisms*
  - *manufacturer must set specifications*



Suggested bacterial limits *(CFU /mL)*

Sampling location	Target	Alert	Action
Raw water	200	300	500
Post multimedia filter	100	300	500
Post softener	100	300	500
Post activated carbon filter	50	300	500
Feed to RO	20	200	500
RO permeate	10	50	100
Points of Use	1	10	100



Pyrogens and endotoxins

- Any compound injected into mammals which gives rise to fever is a "Pyrogen"
- Endotoxins are pyrogenic, come from Gram negative bacterial cell wall fragments
- Detect endotoxins using a test for *lipopolysaccharides (LPS)*
  - *rabbit test detects pyrogens*
  - *LAL test detects endotoxins*
- Ultrafiltration, distillation and RO may remove pyrogens

Group Session

- You are given a schematic drawing of a water system to discuss. List any problems and their solutions





Group Session



CPD



CPD

Questions??



CPD

Thank you


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Water for Pharmaceutical Use

Dr. Mohamed Magdy Arafa
Periodic inspection follow up unit manager

Agenda



1. Water system requirements
2. Water quality specifications
3. Application of specific water to processes and dosage forms
4. Water purification methods

Part 1:
Introduction and treatment



Water for Pharmaceutical Use



Objective:

- Water system reqduirements
- Water quality specifications
- Application of specific water to processes and dosage forms
- Water purification methods
- Storage and distribution systems
- Commissioning, qualification, operation and maintenance

Water for Pharmaceutical Use



Introduction

- Information on Water for Pharmaceutical Use (WPU)
- Quality of water for APIs, finished products, etc.
- GMP for design, installation, operation of systems
- Supplementary to general GMP guidelines
- See also other guidelines, pharmacopoeia, etc.

Water for Pharmaceutical Use



Additional guidelines

- WHO Guideline for Drinking water quality (WHO)
- Water and steam systems (ISPE)
- Bioprocessing Equipment Standard (ASME – BPE 2000)
- European Pharmacopoeia, United States Pharmacopeia, International Pharmacopoeia
- Inspection of Utilities (PIC/S)

Water for Pharmaceutical Use



Principles

- Like any starting material, production of water should conform to Good Manufacturing Practice (GMP) norms
- Potential for microbial growth
- Systems must be properly validated / qualified
- Water for parenteral use should not be contaminated with pyrogens or endotoxins
- Specifications and periodic testing are required

Water for Pharmaceutical Use



Why purify raw water?

- Although reasonably pure, it is always variable due to seasonal variations, regional variation in water quality
- Must remove impurities and control microbes to avoid contaminating products
- Treatment depends on water's chemistry and contaminants, influenced by, e.g. rainfall, erosion, pollution, dissolution, sedimentation, decomposition

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Contaminants of water (2)

Problem minerals

- Calcium, magnesium, copper, aluminium, heavy metals, arsenic, lead, cadmium, nitrates
- Iron, manganese, silicates, carbon dioxide
- Hydrogen sulfide
- Phosphates



Contaminants of water (3)

Microorganisms – Biofilm formation

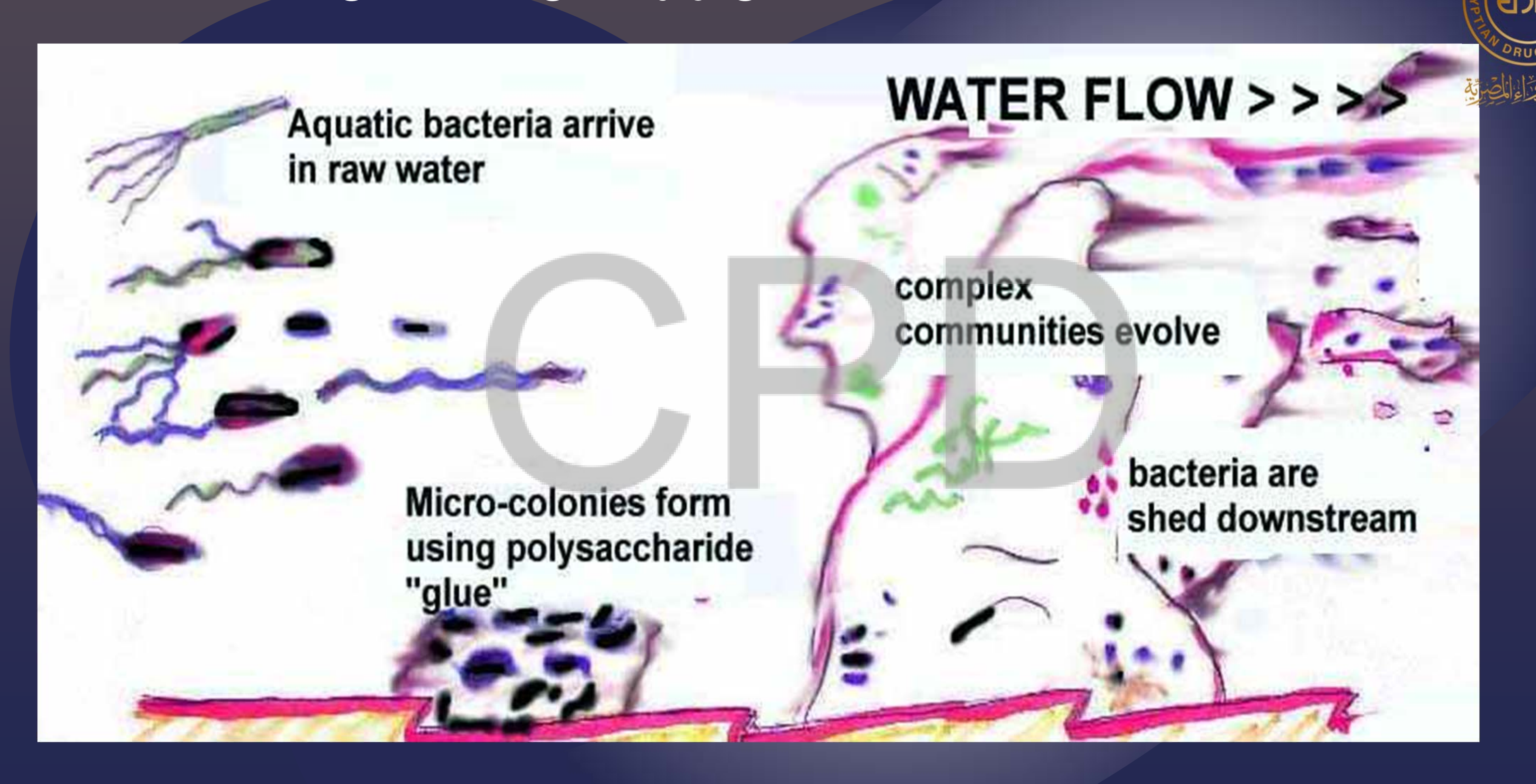
- Protozoa
  - *Cryptosporidium*
  - *Giardia*
- Bacteria
  - *Pseudomonas*
  - *Gram negative, non-fermenting bacteria*
  - *Escherichia coli and coliforms*



Biofilm formation

- Free-swimming aquatic bacteria use *polymucosaccharides* to
colonize surfaces
- Complex communities evolve which shed microcolonies and bacteria

Biofilm formation



Water for Pharmaceutical Use



- Water system requirements
- Water quality specifications
- Application of specific water to processes and dosage forms
- Water purification methods
- Storage and distribution systems
- Commissioning, qualification, operation and maintenance



Background to water requirements and use

- Water is the most widely used substance / raw material
- Used in production, processing, formulation, cleaning, quality control
- Unique chemical properties
  - *Able to dissolve, absorb, adsorb, suspend compounds and contaminants*
- Different grades of water quality available



Background to water requirements and use (2)

- Control quality of water
  - *Production*
  - *Storage and distribution*
- Contaminants, microbial and chemical quality
- Microbial contamination risk and concern
- Water is used on demand
  - *not subjected to testing and batch or lot release before use, therefore has to meet specification "on demand" when used*
  - *Micro test results require incubation periods*



Water system requirements

- Design, installation, commissioning, qualification / validation, operation, performance and maintenance to ensure reliable, consistent production of water of required quality
- Operate within design capacity
- Prevent unacceptable microbial, chemical and physical contamination during production, storage and distribution
- Quality Assurance involved in approval of use after installation and maintenance work

2.



Water system requirements (2)

- Monitoring of water sources regularly
  - *Chemical and microbiological*
  - *Endotoxin level where relevant*
- Monitoring of system performance, storage and distribution systems
- Records of results, and action taken
- Validated sanitization procedure followed on a routine basis

Water for Pharmaceutical Use



CPD

- Water system requirements
- Water quality specifications
- Application of specific water to processes and dosage forms
- Water purification methods
- Storage and distribution systems
- Commissioning, qualification, operation and maintenance



Water quality specifications

Here address *water in bulk* (not for patient administration)

Specifications in pharmacopoeia – relevant to national or international recommendations.

Types of water include:

- Drinking water / potable water
- Purified water (PW)
- Highly Purified Water (HPW)
- Water for Injection (WFI)



Drinking water / potable water

- Must comply with specification (WHO, ISO and national or regional agencies) – regular testing needed
- Supplied under continuous positive pressure
- Defect free plumbing system to prevent contamination
- Could be from public water supply system or natural sources
- Source water quality influences the treatment required

Water for Pharmaceutical Use



Drinking water:

- Natural sources could include:

springs, wells, rivers and lakes

- Treatment includes:

softening, ion removal, particle reduction, antimicrobial treatment





Purified Water (PW)

- Prepared from potable water source
- Meet pharmacopoeia specification for chemical and microbial purity
- Protected from recontamination
- Protected from microbial proliferation

3.3.



Highly Purified Water (HPW)

- Prepared from potable water source
- Specification only in the European Pharmacopoeia
- Same quality standard as WFI including limit for endotoxins, but treatment method considered less reliable than distillation
- Prepared by combination of methods including reverse osmosis (RO), ultrafiltration (UF) and deionization (DI)



Water for Injections (WFI)

- Prepared from potable water source
- WFI is not sterile
- WFI is not a final dosage form
- WFI is an intermediate bulk product
- According to *The International and European Pharmacopoeias* – final purification step should be distillation

Water for Pharmaceutical Use



- Water system requirements
- Water quality specifications
- Application of specific water to processes and dosage forms
- Water purification methods
- Storage and distribution systems
- Commissioning, qualification, operation and maintenance



Application of specific water to processes and dosage forms

- Water used for different stages of:
  - *Washing, preparation, synthesis, production, formulation, control*
- Which grade of water is suitable for a particular stage?

-Consider nature and intended use of intermediate or finished product, and stage at which water is used

- Let's look at types of water and indicate their use



Complete the table

Which type of water?	***Use***
?	Preparation of injectable products
?	Final rinse of equipment after cleaning
?	Final rinse of equipment and components that come into contact with injectable products
HPW	?
Potable water	?

Water for Pharmaceutical Use



CPD

- Water system requirements
- Water quality specifications
- Application of specific water to processes and dosage forms
- Water purification methods
- Storage and distribution systems
- Commissioning, qualification, operation and maintenance



Water purification methods

- Manufacturer to select appropriate method of purification
- Appropriate sequence of purification steps
- Influenced by, e.g.
  - *Water quality specification*
  - *Yield (efficiency) of the system*
  - *Feed water quality*
  - *Reliability and robustness of treatment system*
  - *Supplier support, maintenance and operation costs*

5.1



Water purification system considerations

- Leaching from contact materials
- Adsorption
- Hygienic and sanitary design
- Corrosion resistance
- Leakage
- Proliferation of microbiological organisms

5.1



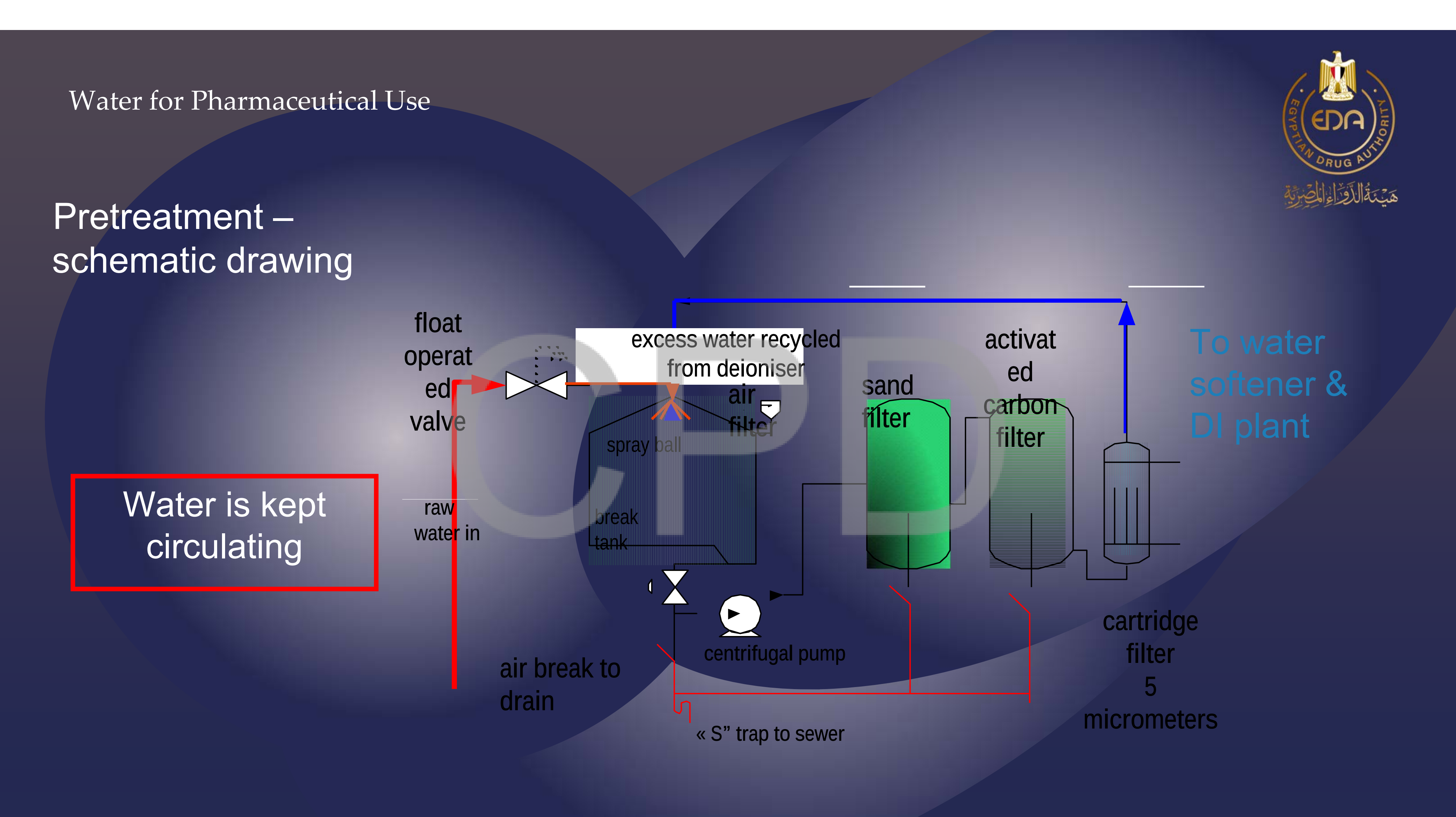
Water purification system considerations (2)

- Tolerance to cleaning and sanitizing agents
- Capacity and output capability
- Instruments, sensors, controls, sampling points
- Space needed for installation and structural loading of premises
- Access needed for maintenance
- Regeneration and sanitization



Pre-treatment steps

- Primary filtration and multimedia filter
- Coagulation or flocculation
- Desalination
- Softening



Water for Pharmaceutical Use
Pretreatment – schematic drawing
Water is kept circulating
float operated valve
excess water recycled from deioniser
air filter
spray ball
break tank
raw water in
sand filter
activated carbon filter
To water softener & DI plant
cartridge filter 5 micrometers
centrifugal pump
air break to drain
« S" trap to sewer
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Water for Pharmaceutical Use



Water pre-treatment complex in a pre-treatment room





Water Softener – schematic drawing

by pass valve

"soft" water to deioniser

brine and salt tank

brine

zeolite water softener
- exchanges
- Ca and Mg for Na

"hard" water in

drain



Chlorine removal (Activated-carbon (AC) filtration or bisulphite)

- AC removes chlorine but bacteria can then grow
- AC filtration can remove organic impurities
- Bisulphite leaves sulphate residues but is antimicrobial



Production of drinking water

- Derived from raw water (e.g. well, river, reservoir)
- Processes may include:
  - *Filtration, softening*
  - *Disinfection or sanitization*
  - *Precipitation*
  - *Inorganic / organic reduction*



Production of *drinking water* (2)

- When done "in-house" – steps used and system configuration documented, and water quality routinely monitored
- Change control in case of changes to system
- Storage of water:
  - *no degradation, ensure turnover, routine testing*
- "indirect impact system" – qualification not needed



Production of drinking water (3)

- System permits draining and sanitization
- Storage tanks:
  - *Closed, with protected vents*
  - *Allows visual inspection, draining and sanitization*
- Care to prevent and control microbiological contamination of sand filters, carbon beds, water softeners
  - *Back-flushing, chemical or thermal sanitization and frequent regeneration, continuous waterflow*



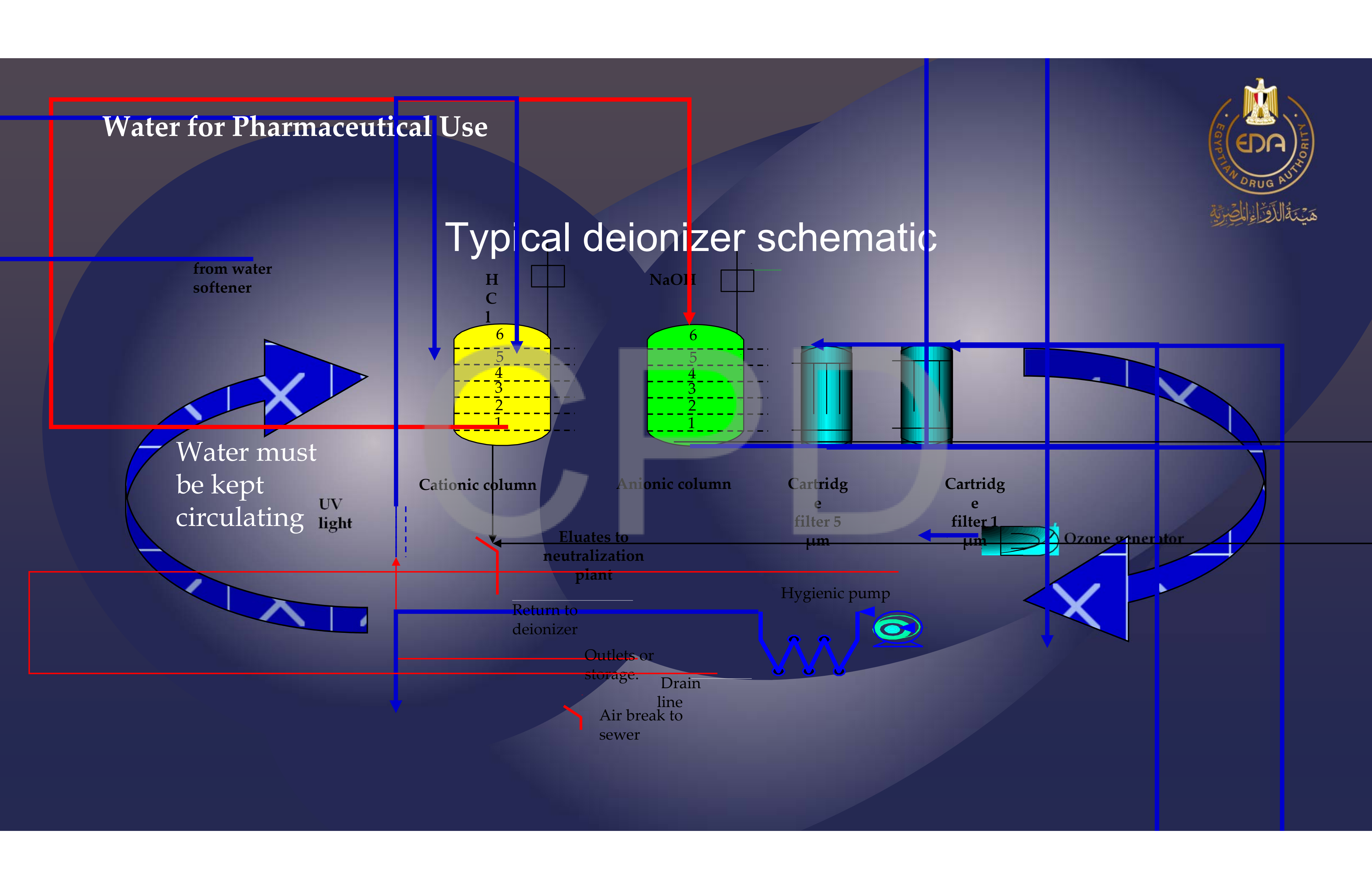
Production of drinking water (4)

- Drinking water supplied by tanker – associated problems and risks
- Required vendor assessment
- Authorized certification activities
- Acceptability of delivery vehicle
- As receiving any other starting material



Water treatment purification stages downstream of the pre-treatment system may include:

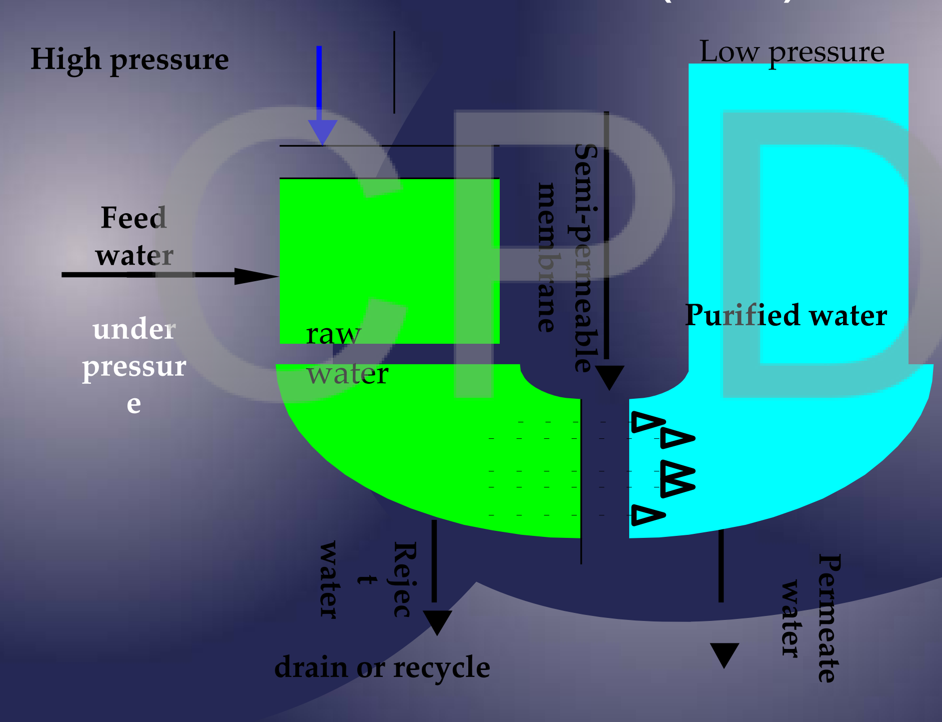
- Filtration
- Disinfection
- Reverse osmosis (RO) or deionization (DI)
- Distillation or ultrafiltration

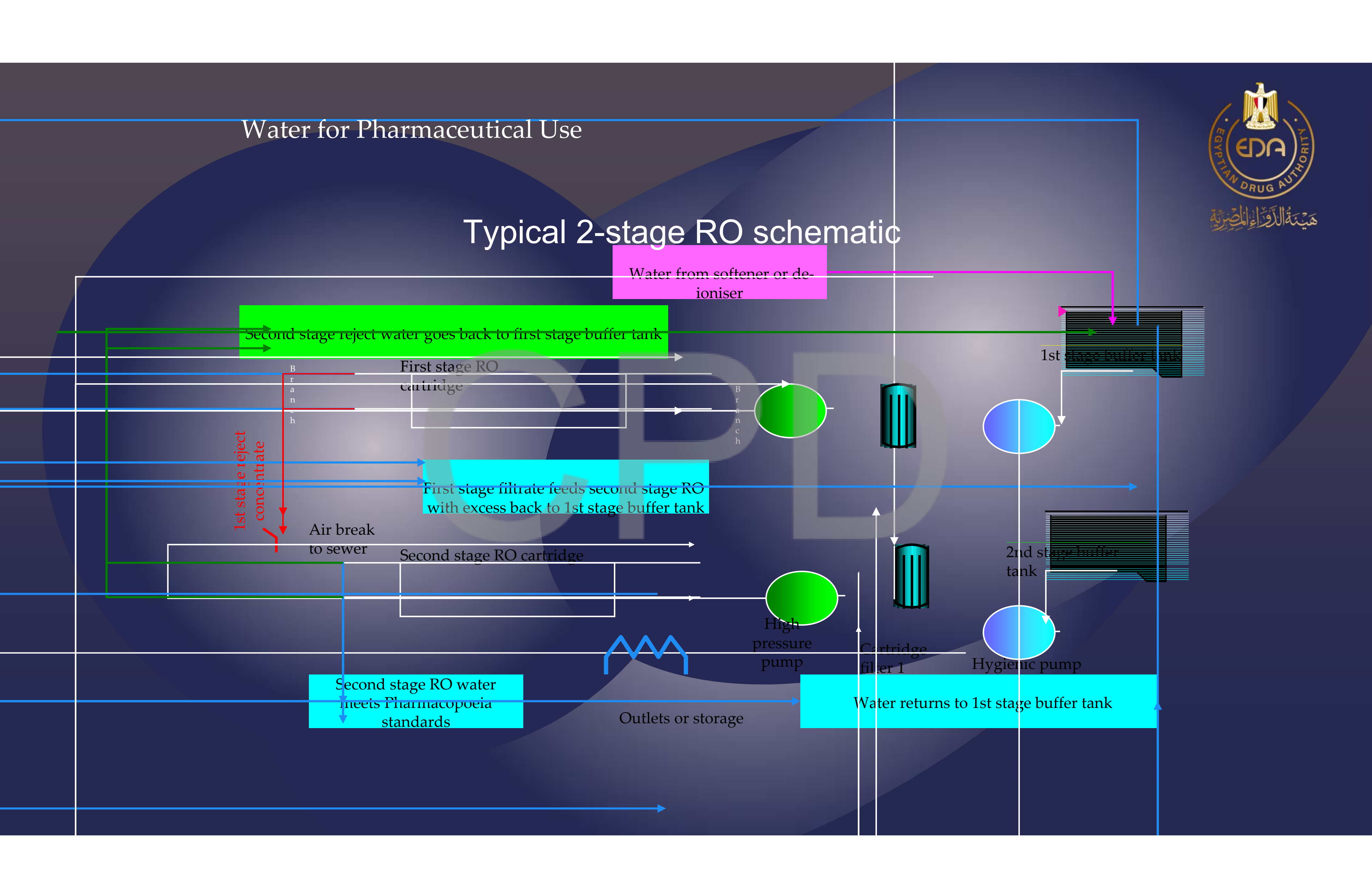


Water for Pharmaceutical Use
Typical deionizer schematic
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EDA
from water softener
H C l
NaOH
6
5
4
3
2
1
Cationic column
Anionic column
Cartridge filter 5 µm
Cartridge filter 1 µm
Water must be kept circulating
UV light
Eluates to neutralization plant
Ozone generator
Hygienic pump
Return to deionizer
Outlets or storage.
Drain line
Air break to sewer



Reverse osmosis (RO) theory





Water for Pharmaceutical Use
Typical 2-stage RO schematic
Water from softener or de-ioniser
Second stage reject water goes back to first stage buffer tank
First stage RO cartridge
Branch
Branch
1st stage buffer tank
1st stage reject concentrate
First stage filtrate feeds second stage RO with excess back to 1st stage buffer tank
Air break to sewer
Second stage RO cartridge
2nd stage buffer tank
High pressure pump
Cartridge filter 1
Hygienic pump
Second stage RO water meets Pharmacopoeia standards
Outlets or storage
Water returns to 1st stage buffer tank
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Typical
R.O







Use of reverse osmosis

- Advantages ????
- Disadvantages????
- Many uses
  - *purified water*
  - *feeding of distillation units or ultrafiltration units*
  - *Water for Final Rinse*
  - *Water for Injections (if permissible)*



Htsynsztzx.%Jqjhywt%Ijntsn;fynts?

Electro De-Ionization is currently the most advanced technology for ion-exchange. With this technology (ultra)pure water can be produced continuously. This high-end technology can have an application in sectors such as: Power plants, process industry and pharmaceutical industry.

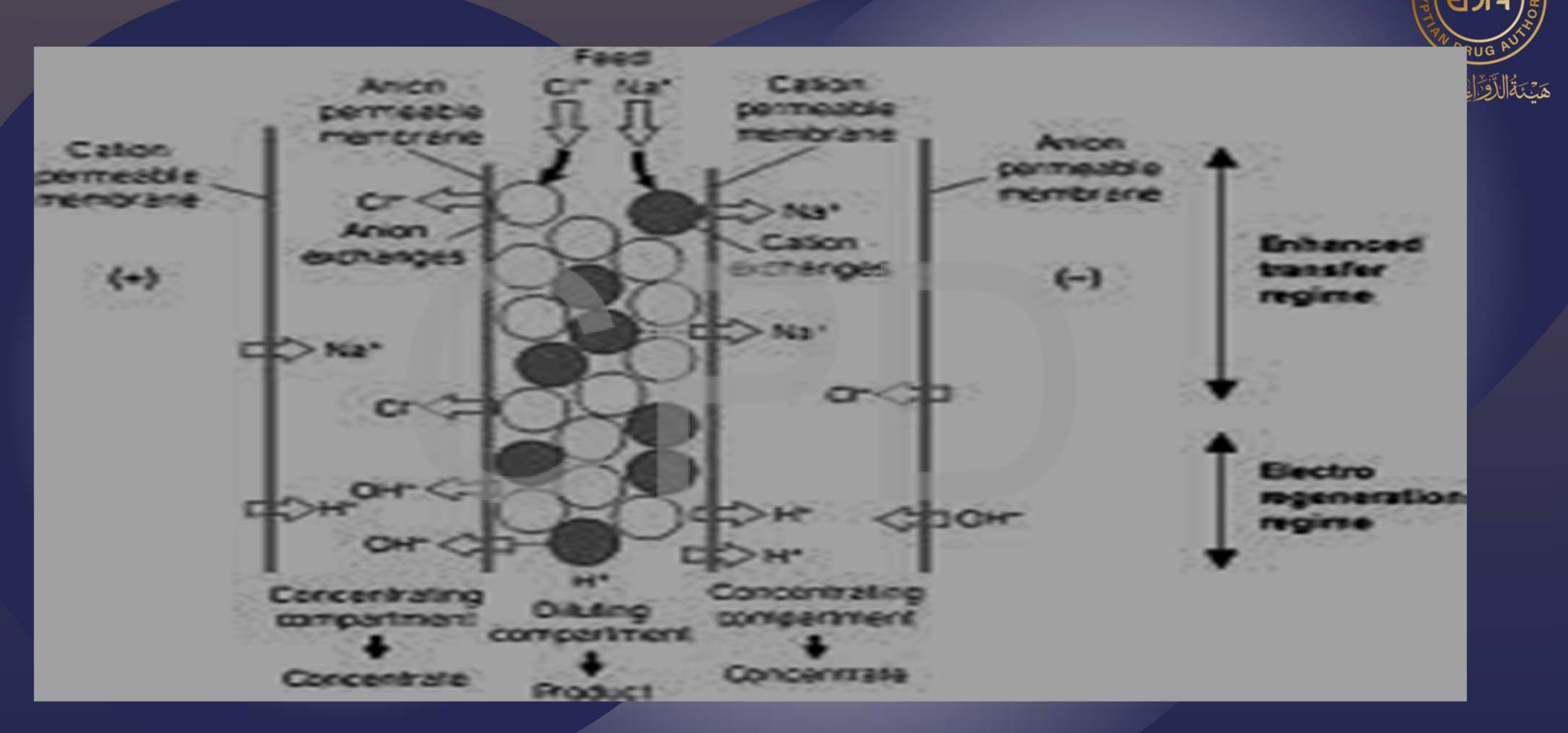
An EDI-unit is usually used as a post treatment of Reverse Osmosis water.

It is a chemically free process that uses electricity and ion exchange resin to produce ultra-pure deionized water.

EDI (Electro de- ionization technique)

Electrode wash
Ultrapure water
Electrode wash
Reject water
Cathode
CEM
AEM
CEM
AEM
Anode
1
2
3
4
5
H^+
H^+
Na^+
Cl^-
Cl^-
Na^+
Na^+
OH^-
OH^-
H_2O
H^+
Cl^-
Na^+
Cl^-
OH^-
H_2O
Electrode wash
Feed RO water
Electrode wash

EDI (Electro de- ionization technique)



EDI (Electro de- ionization technique)





Production of Purified Water (PW)

- Use appropriate, qualified methods for production
- Factors to consider:
  - *Feed water quality and required water quality specification*
  - *Sequence of purification stages needed*
  - *Energy consumption, extent of pre-treatment needed*
  - *Yield and efficiency of unit treatment steps*
  - *Location and design of sampling points*
  - *Appropriate instrumentation for measurements*



Production of Purified Water (2)

- Measurements:
  - *Flow*
  - *Pressures*
  - *Temperature*
  - *Conductivity*
  - *pH*
  - *Total organic carbon (TOC), etc.*
- Appropriately controlled, monitored, records maintained



Production of Purified Water (3)

- Ambient temperature PW systems are susceptible to microbiological contamination – especially when static and periods of low or no demand
- Controls may include:
  - *Maintain flow at all times*
  - *Control temperature in the system (<25 degrees Celsius or more than 65 degree)*
  - *UV disinfection*
  - *Water treatment components that can be thermally sanitized*
  - *Chemical sanitization (e.g. with ozone)*



feed water
micro-filtration
water softener
storage tank
reverse osmosis
de-gasing
storage tank
reverse osmosis
UV-sterilization
mixed bed ion-exchanger
ultrafiltration
storage tank
point-of-use filter

Sodium Bisulphite/
Caustic Soda

Feed

Carbon filter

Softener

RO High pressure pump

Reverse Osmosis unit

Membrane Degasifier

N_2

Purified water tank

Return from P-O-U

O_3

Transfer pump

254 nm Ultraviolet light

Cartridge filter 0.45 micron

EDI Unit

185 nm Ultraviolet light

Booster pump

Polish mixed bed unit

Cartridge filter 0.45 micron

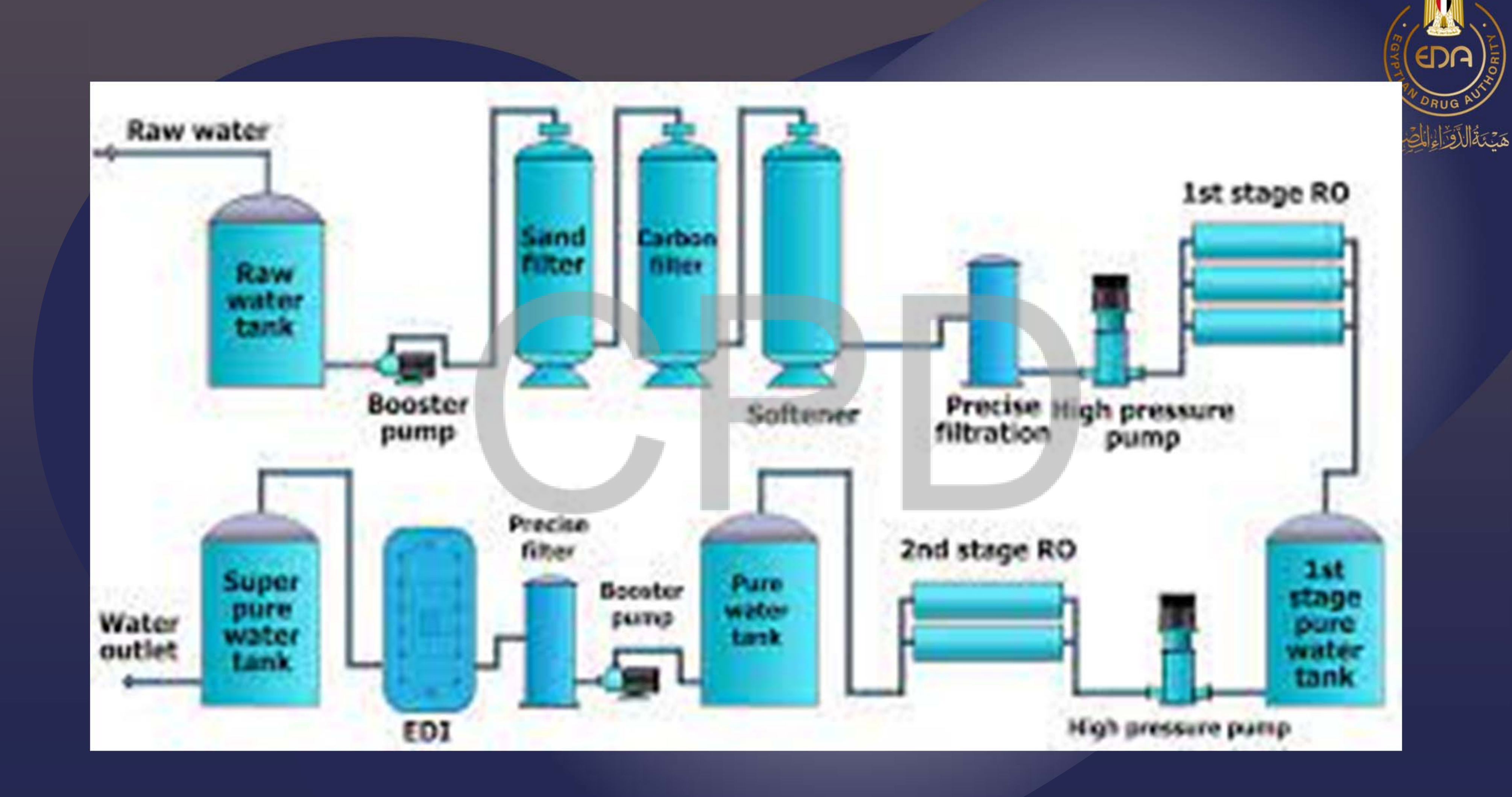
254 nm Ultraviolet light

Cartridge filter 0.2 micron

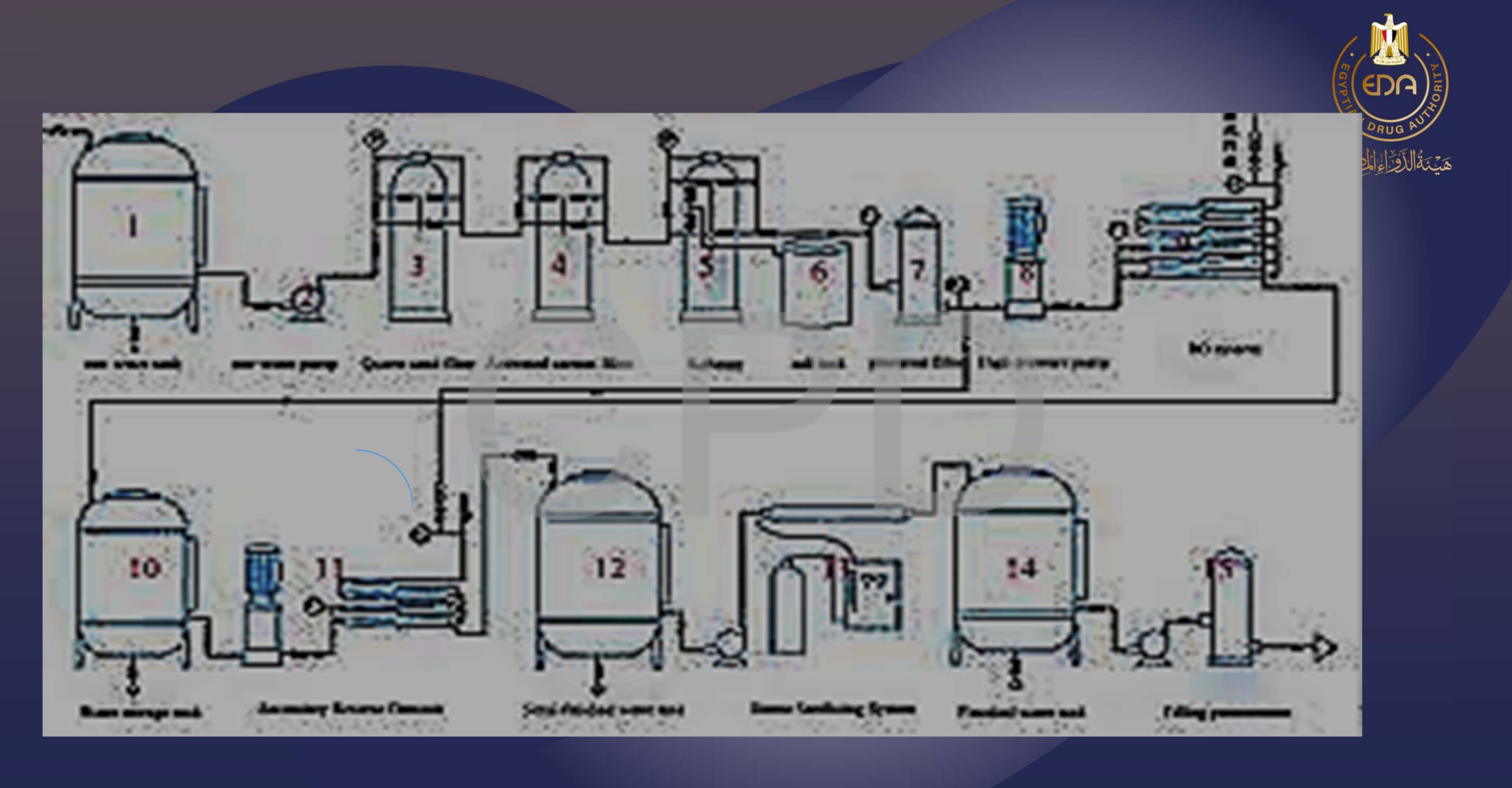
Ultrafiltration Unit

UPW To P-O-U





Raw water
Raw water tank
Booster pump
Sand filter
Carbon filter
Softener
Precise filtration
High pressure pump
1st stage RO
1st stage pure water tank
High pressure pump
2nd stage RO
Pure water tank
Booster pump
Precise filter
EDI
Super pure water tank
Water outlet
CPD
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Production of Highly Purified Water (HPW)

- Use appropriate, qualified methods for production
- Appropriate sequence of techniques
- As for PW
- Processes may include:
  - *Ion exchange*
  - *Ultrafiltration*
  - *Reverse Osmosis*



Production of Water for Injections (WFI)

- Pharmacopoeia requires distillation as preferred technique for final purification step
- Factors to consider:
  - *Feed water quality*
  - *Required water quality specification*
  - *Optimum generator sizing (prevent frequent start/stop)*
  - *Blow-down and dump functions*
  - *Cool-down venting (avoid contamination ingress)*

CPD

Questions??




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Thank
you